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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Lewis A. Conner Memorial Lecture

Primary Hypertension

By GEORGE A. PERERA, M.D.

LEWIS ATTERBURY CONNER, one of the founders and presidents of the American Heart Association, died five years ago in the eighty-fourth year of an illustrious career. As a gentle and beloved teacher of medicine his remarkable qualities of perception, judgment and integrity were recognized by a large audience, and so his influence remains very much alive. In addition, he is memorialized by an annual lecture which I am privileged to give today.

This is not my lecture, but Dr. Conner's. I am obliged, of course, to employ subject matter with which I am somewhat familiar, but the moral is his. Dr. Conner was always keenly aware of the fact that ill persons place their confidence in a physician. So many of his actions conveyed the message that one must assume wholeheartedly the responsibility imposed by this trust. I should like to illustrate this approach through the medium of primary hypertension or hypertensive vascular disease.

THE PHYSICIAN'S RESPONSIBILITY TO HIMSELF

There can be no question that a physician must remain abreast of new information. Basic knowledge is expanding rapidly; technologic advances are being made at an accelerated rate. The doctor cannot possibly advise and care for the sick, honestly and intelligently, that is, unless he continues to educate himself by means of critical evaluation, then selection and, finally, incorporation of new ideas into the framework of his total knowledge.

It is appropriate that we first take a position whether there is such a disease as primary hypertension. If so, is it one condition or comparable to a pile of unassorted mail awaiting its appropriate pigeonhole? Professor Pickering and his associates[1] have been impressed by the role of age, inheritance and as yet unknown environmental factors in determining blood pressure. They have suggested recently that hypertension is no more than "a convenient term for those subjects whose arterial pressures exceed a certain level chosen on arbitrary grounds." Only when the value rises above a critical point for each individual patient, they would submit, are necrotizing arteriolar changes produced. Although most observers agree that average, casually recorded blood pressures of a population sample tend to rise with age, the resultant curve (fig. 1) is made up of multiple components. That primary hypertension is an abnormal state seems inescapable, when one considers its onset (almost if not always before the age of 50, and occasionally quite abrupt), its complications (arteriolar damage is uncommon in those older subjects with predominantly systolic hypertension related to

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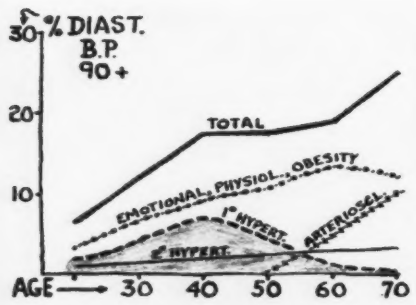

FIG. 1. Percentage of persons in different age groups with initial "casual" diastolic blood pressure of 90 mm. Hg or above, and the cause of the elevated pressure (based on 1000 ambulatory patients in Vanderbilt Clinic).

arteriosclerosis of the aorta) and its definite effect on life span in the majority of instances (average age at death, 52).

Broadly speaking, we must admit that some patients with primary hypertension do remarkably well. They are generally female, apt to be overweight, hyperkinetic and emotionally labile, sometimes with high "casual" blood pressure readings but usually with considerable fluctuation on repeated measurement. They possess, if you will, a big neurogenic and vasomotor component. They die somewhat later in life with cardiac hypertrophy and arteriosclerotic complications out of proportion to their weight and age. In contrast to this *arterial* type are those whose clinical course points towards an *arteriolar* emphasis, encountered more often in males and the underweight, with rather fixed blood pressure levels and earlier death after arteriolar damage reflected in the renal and retinal areas. However, the engaging fact is that the arterial picture, at any point along the line and without warning, may suddenly shift to the arteriolar; the picture may be mixed.

Although in general the mean arterial tension is higher in those patients who are clinically in the arteriolar or in the accelerated ("malignant") phase, I cannot agree that the associated pathologic alterations are solely a function of pressure. The accelerated phase, encountered in some 7 per cent of those with primary hypertension and with an entirely different sex incidence, can sometimes begin de novo without antecedent hypertension, its full-blown clinical picture may appear without a further rise in pressure, and it has developed, in rare but documented instances, during periods in which vascular accidents have rendered the patient normotensive. Patients in the accelerated phase usually exhibit less labile blood pressure readings, being unaffected by rest or sedation; sodium restriction may be followed by major decreases in serum sodium concentrations related to the renal damage, yet this occurs without a fall in blood pressure, unlike a group without complications; and their clinical pattern and pathology are almost reminiscent of that seen in periarteritis nodosa. The evidence at hand leads me to feel that the accelerated phase is not just a quantitative change in tempo but rather the superimposition of a qualitatively different process. Perhaps when a certain type or degree of renal damage ensues, the kidney either fails to participate in some essential manner (as suggested by preliminary reports of necrotizing arteriolitis after removal of both kidneys in animals) or sends out its own damaging agent.

Having been guilty already of some speculation, may I suggest also that until underlying mechanisms are clarified better, we may confuse ourselves by applying terms that are prognostic and by artificial and arbitrary groupings into too many types and gradations of disease. Someone once advised young John Adams, "Give life an opportunity to arrange itself." And so let us dispense for the time being with such adjectival preconceptions as *benign*, *malignant*, *diencephalic*, *endocrine*, *pseudo*-this-and-that, until we have grasped the whole. Recall that primary hypertension remains a label of exclusion.

A physician has a responsibility to be curious, an attitude termed by Samuel Johnson a "certain characteristic of a vigorous mind." Curiosity leads to careful exploration, to the marshaling of all the evidence, and ultimately to the acquisition of new knowledge some of which may be useful within our time. Furthermore, the challenge engendered by

curiosity makes the practice of medicine more enjoyable. To be concerned only with treatment and not with pathogenesis can lead to mistakes in diagnosis and missed opportunities. The fruits of curiosity, transcribed into active investigation at the bedside, in the record room, and through simple as well as complex procedures in the laboratory, have brought to light a number of facts of considerable importance. We no longer remain in total darkness, but the visual ceiling is still low. With reference to pathogenesis, where do we stand today? One might summarize our present position in the following manner: (1) the cause of primary hypertension has not been established; (2) the majority of disorders associated with secondary hypertension stem from the central nervous system, the adrenals or the kidneys; (3) almost every type of secondary hypertension has its experimental counterpart; (4) from the experimental standpoint, the role of the kidney remains in the ascendancy; the most noteworthy recent line of investigation has been the production of an elevated blood pressure by removing both kidneys (renoprival hypertension) in addition to the conventional Goldblatt and related technics and (5) primary hypertension appears to be a genetic disorder, and hence there is justification—as in diabetes or gout—for thinking along the lines of a biochemical aberration, an error in metabolism. It is tempting, therefore, to think that a group of persons have an inherited susceptibility to vascular alteration as the result of a metabolic derangement. Then in some of them, at varying rates and to variable degrees, there is increasing participation of the kidneys which elaborate or destroy some chemical substance. The end-result is the progressive cardiovascular disease we know as primary hypertension.

The Physician's Responsibility towards an Illness

If we are to do justice to an illness, it is obvious that we must appreciate its existence, consider the various diagnostic possibilities before settling on the correct answer, make an appraisal of the severity of the disorder and relate the findings to the natural history of the disease.

Primary hypertension is characterized by hypertension. Unfortunately, as yet, no other single clinical sign or symptom, or combination for that matter, is pathognomonic. Therein lies our first difficulty. Hypertension, I would suggest, is not a term to be employed just for high blood pressure. There are numerous real or apparent elevations of blood pressure which are not indicative of hypertensive disease, such as those produced by environmental and psychogenic stimuli, the falsely high readings in the obese arm which can raise the recorded value as much as 15 mm. of mercury, and sclerosis of the aorta which can probably give rise to levels sometimes reaching 200/100. At the present time there is considerable evidence to support the view that diastolic pressures of 90 should be regarded with suspicion and to define hypertension as the repeated finding of a casual diastolic pressure of 90 mm. of mercury or more after the exclusion of those with transient rises, those with marked obesity (unless values are in excess of 105) and those with possible arteriosclerotic causes (unless values are in excess of 100).[2] The fact that hypertension is defined variously and that its incidence is reported by some to be 5 to 10 per cent, by others to exceed 50 per cent of the population, illustrates the difficulty. The fact that rest, fever or vascular accidents may temporarily obliterate hypertension adds to the confusion. The real issue is to differentiate the healthy from those who are ill; this is not always accomplished readily but we must assume the responsibility for as accurate a diagnosis as possible.

Primary hypertension, the major cause for an abnormal elevation of blood pressure and which we believe to be present in about 5 per cent of the adult population, may be defined as hypertension which is not secondary to a known primary pathologic process. This is not the place to repeat all the problems of differential diagnosis or all the vagaries of this condition. However, certain aspects deserve emphasis or restatement if we are to apply our knowledge of illness to the care of

the patient, if we are to substitute "hypotheses derived from experiment for dogma built on superstition."[3]

The exact role of the blood pressure in contributing to the development of complicating pathologic changes has not been settled. Longer studies and more information of diurnal fluctuations are essential. Yet patients are frightened and their life programs interrupted only on the basis of the height of a mercury column as recorded in office or clinic. The view that single or even multiple "casual" readings of the arterial tension are of little prognostic value has been expressed repeatedly for 30 years but has been generally ignored. The fact remains that it is the lability or stability of blood pressure which matters. In an experience with over 3,000 patients with primary hypertension, 500 of whom were followed until death, we have been unable to relate the initial blood pressure level, the maximum or even the mean "casual" level to symptoms, rate of progression or the subsequent development of complications. On the other hand, fixed high diastolic levels which remained elevated following rest or sedation were associated usually with a shortened total duration of disease, a higher incidence of arteriolar complications and an earlier age at death. Said another way, high "resting" blood pressure values or repeated readings that show little deviation represent the more ominous prognostic sign.

Another area of regrettable confusion centers about the accelerated phase of primary hypertension. I am reminded of Lewis Carroll's Humpty-Dumpty who said to Alice, "When I use a word it means just what I choose it to mean." There seem to be a few remaining Humpty-Dumpties in the hypertensive world who define the accelerated phase only on the basis of the eyeground changes, on the presence of nitrogen retention or on the height of the diastolic blood pressure; yet others include (or fail to exclude) the late stages of many types of primary renal disease. The accelerated phase is characterized clinically by an accelerated velocity, progressive damage to the renal area and death in uremia unless the course is terminated along the way by coexistent brain or heart damage. I must emphasize that measurements of velocity cannot be made on the basis of a single observation but require enough points on the curve to document the feature of progression. How good is this characterization? It is valid only if the patient does not have some other cause of kidney damage, such as unilateral renal disease, polycystic disease or periarteritis nodosa. It is valid only if the ultimate pathologic picture is one of a necrotizing arteriolitis involving particularly the kidneys, retinae, pancreas, liver and periadrenal areas. For greater accuracy, therefore, postmortem studies are necessary; clinically one can only be correct about 9 times out of 10, as a few patients will have an indistinguishable course due to extensive arteriolosclerotic alterations in the kidneys.

The majority of patients in the accelerated phase show extensive retinopathy, usually with papilledema, but on occasion the eyeground changes are absent or minimal, or if present may even regress. The presence of papilledema is supportive evidence in the face of progressive renal damage; it is not essential and, indeed, not always diagnostic as it has been encountered infrequently in subjects with less advanced disease. The response of the retinal lesions to treatment does not prove that the underlying process has been altered, any more than relief of headache indicates cure of brain tumor, unless one can establish that the basic pathology has also been reversed. Nor is nitrogen retention obligatory for a diagnosis; it is absent in the early stages and, although an almost inevitable late consequence, may be demonstrable in some patients with nephrosclerosis alone or may appear as a consequence of congestive failure. Finally, it is possible to develop and to die of the accelerated phase of primary hypertension with only minimal elevations of blood pressure.

To summarize this point of view, we should suspect the accelerated phase when our patient with primary hypertension develops signs of progressive renal involvement, accompanied frequently, but not always, by retinopathy and papilledema. Our clinical

diagnosis will be about 90 per cent accurate and only necropsy will improve our "batting average." Diagnosis or prognosis based on eyegrounds alone will be far less accurate. For example, using the Keith-Wagener-Barker classification,[4] patients in the accelerated phase may fall into either groups II, III or IV; although helpful descriptively, this system of classification of the retinal changes may yield erroneous results, especially if one favors the concept, as I do, that the accelerated phase represents some superimposed pathogenetic factor at work and not just a more intensified disease.

Once an illness has been recognized and categorized, it is almost an obligation to be as familiar as possible with its average untreated behavior as well as with all of its individual variations. Then, and only then, can the physician determine best how far along the road his patient has traversed, how far he has to go and whether his speed can be slowed or his path channeled in some other direction than the inevitable end. Perhaps this can be illustrated to advantage by a diagram (fig. 2) based on the histories of 500 patients with primary hypertension, some followed from before onset, others from an uncomplicated phase, all followed until death.[2] Speaking in terms of averages, here we have a chronic illness beginning as a rule in early adult life, persisting for a period of two decades before its complications cause death at an age 15 to 20 years less than the normal life expectancy. Here we have a disorder in which more years are spent without significant symptoms or complications than with. Here is a condition which shortens life through its effects on the heart and blood vessels, through cardiac hypertrophy, arteriolosclerosis and augmentation of the arteriosclerotic process. To prove that one has altered the course of patients in the accelerated phase, a statistically significant series of patients must be studied for well over two years; to prove that the course of patients in the uncomplicated phase has been altered, an adequate series must be followed for a period in excess of 20 years. The proper evaluation of therapy must rest on comparison with this portrayal of an average life story—it is our responsibility to know it.

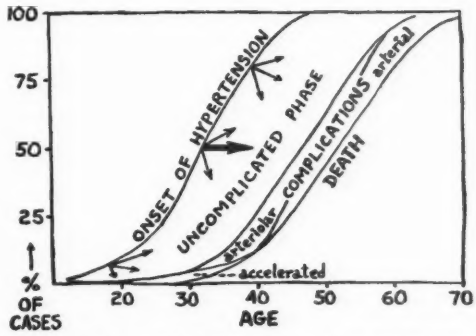

FIG. 2. Schematic diagram, based on 500 patients with primary hypertension, indicating age of onset, predominant nature of complications, age at death, possible courses of individual patients (thin arrows) and the course of the average patient (thick arrow).

THE PHYSICIAN'S RESPONSIBILITY TO HIS PATIENT

At first glance, the physician's obligation towards a patient is to cure the disease from which he suffers and to forestall his possible disability or death. Such an objective is certainly desirable, but when applied to primary hypertension and many other chronic disorders, it is unrealistic and incomplete. It is unrealistic, in my opinion, because a fulfillment is implied which is not always within our reach; it is incomplete because of its emphasis on material aspects to the neglect of the individual and his environment. Our additional obligations are to relieve the body and mind to the best of our ability, to make the road easier and to be as concerned with the impact of disease as we are with the disease itself.

Not long ago, the family physician would look at the tongue or feel the pulse. He might provide sympathetic understanding, but could offer little else beyond bleeding or a purge. The doctor of today has more advanced methods of insight into the interaction of personality, environment and disease, but in addition he is now equipped with the means to study almost every organ and function of the body, with an ingenious array of scientific apparatus and with a host of powerful drugs

and operative technics. His responsibility has grown proportionately. He must use this modern knowledge with balance and perspective. He must become thoroughly familiar with the tools of his trade, their action, their limitations and their dangers. He is now in a better position to do good but also has many more opportunities to do harm. If he is not to do injustice to his patient, he must recognize that the best medicine is practiced in an environment in which "the atmosphere is experimental, the mood is inquiring, the goal is understanding."[3]

Let us relate this discussion to the present-day management of the patient with primary hypertension. Our foremost obligation is reassurance, administered with sympathetic and compassionate understanding, especially when we are beset by some authorities who strive to make people "scared of living and fear'd of dying." More persons live with hypertension than die of it.

It is not possible to remove the cause for it is not known. Efforts to prevent the complications of hypertensive disease are still in an experimental stage; the experiment is in progress but has not been concluded. Nevertheless, means are available in many hypertensive subjects to relieve symptoms, to lower the blood pressure, to modify such complications as congestive failure and retinopathy and to prolong the life of some individuals in the accelerated phase. These achievements, milestones in themselves, must be weighed against the relative risks and the disruption of the patient's way of life.

Thus, it would seem to me that the following approach to the management of patients with primary hypertension may have a rational basis at the present time. After clarification that hypertension is present, after the exclusion of other causes and after thorough evaluation of the damage done, it is appropriate to spend a great deal of time devoted to reassurance, preparing the patient for what he will hear and read and educating him to accept his situation with optimism and hope. Invalidism and undue restriction should be avoided unless necessitated by the complications present, and it is proper to restore the red meat, caffeine and small doses of alcohol which may have been curtailed by others. One should try to combat obesity. Because of its convincing experimental associations and its mild effects on symptoms and blood pressure, a moderately low sodium diet may be suggested for patients without complications, but established gain cannot be substantiated. Salt restriction is of definite benefit for such manifestations as retinopathy and congestive failure; however, it should be carried to extremes in but rare instances, for only brief experimental periods and with awareness of the dangers of excessive sodium loss when there is renal damage.

Mild sedatives and the Rauwolfia alkaloids in either crude or purified form may be of benefit in some restless and anxious patients in the uncomplicated phase. The Rauwolfia compounds are reasonably safe but must be watched lest they provoke undue mental depression. Occasionally they induce postural hypotension, and very rarely edema, even congestive failure, may appear presumably through abnormal salt and water retention. Mild hypotensive action, bradycardia and tranquilizing effects occur in some labile and hyperkinetic patients, but not all; these drugs are seldom of any value in individuals with more advanced disease, even as an adjunct to other pharmacologic agents. Headaches may be a complaint at some time in about two thirds of a hypertensive population, although they bear little relationship to the exact blood pressure level. It is amazing how frequently they respond to time, suggestion, mild analgesics, caffeine or sleeping with elevation of the head of the bed. Only infrequently are other drugs necessary, and only after simpler measures have been given an adequate trial.

For practical reasons, the ergot derivatives may be discarded; they are weak in action and temporary in their effects. Under controlled conditions and after adequate baseline periods, it is unusual for any veratrum compound to lower the blood pressure significantly without invoking some degree of nausea and vomiting. Hydralazine produces a hypotensive response in the minority of patients to whom we have

administered it. Its variability, its many side effects including cardioacceleration, mental symptoms, anemia and sensitivity reactions similar to disseminated lupus, make it most unsatisfactory for solitary use, and in combination with other drugs it has rarely produced convincing additive action. Despite reported calculations, indicating that hydralazine usually increases the cardiac output but without affecting the coronary flow or heart muscle nutrition, the fact remains that patients with coronary artery disease may develop cardiac pain or show an increased frequency of anginal attacks.

Ganglionic-blocking agents such as the hexamethonium compounds and pentolinium share the ability of sympathectomy to modify some of the manifestations of the accelerated phase of primary hypertension. There is no question that blood pressure can be lowered, symptoms relieved, severe retinopathy improved and congestive failure helped—the last probably through redistribution of blood to the splanchnic bed. We must accept the fact, at least in this stage of the disease and providing treatment has been instituted before there is much nitrogen retention, that the lives of some patients have been lengthened and that they have been able to lead a more comfortable existence. Insufficient time has elapsed, when results are compared with the natural history of the untreated disorder, to make definitive statements about drugs or surgery employed in earlier phases.

Instead of the customary technics of evaluating improvement on the basis of changes in blood pressure and manifestations of disease, the advantages and disadvantages of one form of therapy should be weighed against those of other forms as well as against control groups. For example, the ganglionic blockers require daily titration, produce undesirable side effects through blockage of parasympathetic pathways, whereas the morbidity of sympathectomy is low. In 30 consecutive patients with azotemia, in whom congestive failure was not contributing, pentolinium, in doses sufficient to lower the blood pressure to normal or near normal, failed to improve the renal insufficiency. Sympathectomy also has severe limitations and risks in the presence of significant renal damage and nitrogen retention. Few of our patients could be maintained on drugs for long periods; sympathectomy requires no continued daily dosage. Finally, whereas the ganglionic blockers have been used for 4 or 5 years at best, observations on the results of surgery began more than 16 years ago; survival figures indicate that about 50 per cent of patients in the accelerated phase who qualified for operation lived for a mean period of close to five years,[5] far better than almost anyone's control group and an achievement not yet approached by pharmacologic methods primarily because these drugs have not been available for this length of time.

There continues to be a place to offer and sometimes urge sympathectomy for patients who develop evidence of arteriolar damage, particularly if they are clinically in the accelerated phase and before too much renal damage. The evidence leads me to feel that it is the best form of treatment at present. The ganglionic blockers may also be used but one must look upon them—until more facts are known—as experimental alternatives for those who are not candidates or refuse the surgical approach. There are absolutely no data available as yet to indicate that any of these regimens are specific or that procedures aimed at the autonomic nervous system will solve more than a fraction of the problem of primary hypertension. It is my guess that ganglionic-blocking drugs may equal the record of surgery but not exceed it.

The point of these references to my personal attitudes and practices of the moment is not that they are correct or that others should adopt them necessarily. Rather, they serve to illustrate that one must distinguish between established fact and a continuing experiment, and that it matters less what is done than the judgment of the physician who undertakes the program. The use of any therapeutic measure calls for thorough familiarity with the agent. It must be considered not only in relation to the disease but also to the patient, his reaction to his illness and his particular individual qualities and problems.

The story of primary hypertension is incomplete. Its nature remains obscure, although its natural history is beginning to unfold. Its therapy is nonspecific and still experimental. But until and even after our inquiries have borne fruit, let us keep in mind that some 1900 years ago Paul advised the Galatians: "Let us not be weary in well doing." And whether applied to ourselves or to disease or to our patients, we must not forget the advice of Dr. Conner to assume completely the responsibilities imposed upon us by our patients' trust.

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Albuminuria in Congestive Heart Failure

By GEORGE A. RACE, M.D., CHARLES H. SCHEIFLEY, M.D., AND JESSE E. EDWARDS, M.D.

Albuminuria may be an integral part of the picture of congestive heart failure. Of 161 patients in whom the histologic renal findings were considered to be either normal or to be of such a nature as not to be responsible in themselves for albuminuria, and in whom clinically obvious causes for albuminuria had been eliminated, 141, or 88 per cent, had albuminuria. The incidence of albuminuria was about equal among the various types of heart disease when heart failure existed. A trend existed for the grade of albuminuria to parallel the grade of heart failure. Based on a study of 21 patients, there seemed to be a correlation between the grade of albuminuria and the group of hypertension, according to funduscopic examination. No correlation was found between the grade of albuminuria on one hand and the systolic or diastolic values for blood pressure, the known duration of elevated blood pressure, the grades of hematuria or the values for blood urea on the other hand. Among the 161 patients with heart failure in our group 1 (kidneys either normal or containing lesions not judged to be causes for albuminuria), there was no predominant renal lesion associated with any one cardiac lesion.

ALBUMINURIA has been observed commonly in the presence of congestive heart failure. In a given case of congestive heart failure, the presence of albuminuria raises the question as to whether it is a reflection of independent renal disease or simply one aspect of the cardiac failure.

A review of the literature from 1916 through 1954 failed to reveal any pertinent studies carried out with necropsy material that would resolve this question.

MATERIAL AND METHODS

In this study, basic data were extracted from clinical and necropsy material. The chief types of data were: (1) the various types of heart disease as determined at necropsy; (2) histologic renal findings, which revealed either a renal disorder or normal kidneys; (3) the presence and grades of albuminuria and (4) gradations of heart failure. These four sets of data were derived independently, and the comparisons were made from them after all data had been accumulated.

The study is based on the clinical records of all patients at the Mayo Clinic for whom a diagnosis of congestive heart failure had been made during the final illness in the period 1948 through 1953, and who had come to necropsy.

The clinical bases for the diagnosis of congestive heart failure were first verified by a review of the clinical records. Next, for a given case to be eligible for inclusion, it was necessary that urinalysis had been done at the same time as the examination at which a diagnosis of congestive heart failure had been made. Clinically, there was no obvious cause for albuminuria other than congestive heart failure at the time congestive heart failure was diagnosed.

In the present study, albuminuria was graded on the basis of 1 to 4. The Section of Clinical Pathology of the Mayo Clinic, in which these urinalyses were made,[1] has determined grade 1 albuminuria to represent 5 to 20 mg. of albumin per 100 ml. of urine; grade 2: 30 to 50 mg. per 100 ml.; grade 3: 60 to 90 mg. per 100 ml.; and grade 4: more than 100 mg. per 100 ml.

On the basis of the above criteria, 212 cases of congestive heart failure in which necropsy had been done were studied. The clinical records were reviewed and pertinent information was extracted. The necropsy records were reviewed for the classification of the heart disease, the manifestations of congestive heart failure and evidence of gross abnormalities of the kidneys.

On the basis of the clinical and pathologic data, a system of gradation of heart failure was evolved. The heart failure of each patient was graded from 1 to 4. In addition, the heart disease of each patient was placed in one of the following six categories: (1) mitral-valve disease, with or without aortic stenosis; (2) coronary arterial disease, with or without hypertension; (3) isolated aortic-valve disease; (4) hypertensive heart disease; (5) myocardial hypertrophy of unknown cause and (6) miscellaneous.

A histologic examination of the kidneys of each patient was then made, independent of any knowledge of the clinical history or of the gross pathologic findings. The cases were divided into two groups, depending upon the renal histologic findings.

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Abridgement of thesis submitted by Dr. Race to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

Group 1 was comprised of 161 cases in which the kidneys were considered either to be normal or to contain lesions not thought to be of such a nature or degree as to be obvious causes for albuminuria. Four different categories of renal findings were included in group 1: (1) a normal kidney; (2) benign nephrosclerosis; (3) benign nephrosclerosis associated with small scars of either healed infarcts or healed pyelonephritis and (4) only small scars of either infarcts or pyelonephritis.

Group 2, comprising 51 cases, included those in which the renal lesions were of such a nature or degree that they could have been considered responsible for albuminuria. Six different categories of renal conditions were included in group 2: (1) acute infarction; (2) malignant nephrosclerosis; (3) intercapillary glomerulosclerosis; (4) unilateral renal atrophy; (5) nephrosclerosis associated with hydropic tubules; and (6) a miscellaneous group.

The major comparisons of this study were made only on the cases in group 1.

Results

The 61 female patients in group 1 were from 5 days to 89 years old, the mean being 64 years. Of the 100 male patients, the youngest was 17 and the oldest was 89 years old, with a mean of 62 years.

The incidence of albuminuria, as well as the distribution according to the grades of albuminuria, was almost identical between the two sexes. Albuminuria occurred in 86 per cent of the males and in 90 per cent of the females of group 1.

The types of renal conditions among the 161 patients of group 1 were as follows: 34 had normal kidneys, 68 showed the lesions of benign nephrosclerosis alone, 48 had benign nephrosclerotic lesions associated with small healed infarcts or pyelonephritic scars and 11 showed evidences of small scars only.

Twenty patients, or 12 per cent, of the 161 forming group 1 had no albuminuria, as compared to 141, or 88 per cent, with albuminuria. Albuminuria of grade 1 or 2 was found most frequently in the patients with congestive heart failure. One hundred and fifteen of the 161 patients in group 1, or 71 per cent, had such a degree of albuminuria. None of the patients with scars of healed pyelonephritis or infarction had albuminuria of grade 3 or grade 4, whereas the patients in each of the other categories of group 1 including that of normal kidneys had albuminuria ranging from grade 1 through grade 4.

All but two of the 51 patients (96 per cent) in group 2 had albuminuria. The only two patients in group 2 who did not have albuminuria were among the 17 with acute infarction of the kidney.

The findings in this study also showed that there was no predominant renal lesion associated with any one cardiac lesion. Normal renal findings as well as the histologic evidence of nephrosclerosis and the small healed scars of pyelonephritis and renal infarction were found in each of the six categories of heart disease.

In group 1, the types of heart disease, together with the numbers of cases in each category, are seen in table 1. It is readily apparent that the incidence as well as the distribution of the grades of albuminuria in the various categories of heart disease was roughly equal. Among the four largest categories of heart disease in this study (mitral valvular disease with or without aortic stenosis, coronary arterial disease, isolated aortic valvular disease and hypertensive heart disease), representing 90 per cent of the total number of cases, there was a spread of only 9 per cent—

Table 1.—*The Incidence and Grades of Albuminuria in Group 1 According to the Type of Heart Disease*

Type of heart disease	All cases	Patients with albuminuria					
		Grade				Total	% of all cases
		1	2	3	4		
Mitral-valve disease with or without aortic stenosis	26	8	11	4	1	24	92
Coronary-artery disease with or without hypertension	76	22	37	5	2	66	87
Isolated aortic-valve disease	26	5	11	3	3	22	85
Hypertensive heart disease	17	1	9	3	3	16	94
Myocardial hypertrophy; etiology unknown	11	2	5	1	0	8	73
Miscellaneous	5	2	2	1	0	5	100
Total	161	40	75	17	9	141	88

rom 85 to 94 per cent—in the occurrence of lbuminuria. Likewise, in the foregoing four ategories, all four grades of albuminuria were epresented.

In the literature, considerable emphasis is aid on the relatively higher incidence of al-uminuria in congestive heart failure associated vith hypertensive heart disease as compared vith the prevalence of albuminuria in the resence of heart failure on the basis of other ardiac classifications. Among others, Ehr-ström[2, 3] and Brucer and Robinson[4] have made this point.

The figures reflected in table 1 show that there is no preponderance of albuminuria in any one category of heart disease.

On the basis of clinical and necropsy findings, the conditions represented in the study were divided into four grades of heart failure. This gradation was established independently of urinary and histologic renal findings.

In appraisal of this correlation between the grade of albuminuria and the grade of heart failure, it must be emphasized that many of the factors involved are dependent upon individual interpretations. Thus, the original descriptions of the physical examination depended on the astuteness of the observer. On occasions, the findings of one clinician varied from those of another examiner, and the choice of the finding to be quoted was subject to the discretion of the person abstracting the clinical history. Accurate necropsy reports required comparable levels of recording. Moreover, the balancing of clinical and postmortem findings again permitted the intrusion of the human factor. It is also reasonable to assume that the grading of albuminuria in the laboratory is subject to human error. Thus, each of the two components in this correlation is liable to probable error of one grade, plus or minus.

Theoretically, if this correlation were per-fect, all patients with grade 1 albuminuria would have grade 1 heart failure, all patients with grade 2 albuminuria would have grade 2 heart failure and so on.

Thirty-one patients were classified as having grade 1 heart failure; 66 patients as having grade 2; 51 patients as having grade 3; and 13 patients showed evidences of grade 4 heart failure. Hence, the heart failure of the large majority of patients was of grade 2 and grade 3.

Of the 31 patients with grade 1 heart failure, 23, or 74 per cent, had albuminuria of grade 1 or 2. None with grade 1 heart failure had albuminuria of grade 3 or 4. Among those patients with grade 2 and grade 3 heart failure, a preponderance had albuminuria of grade 1 or 2, less of 3, and still less of 4. None of the 11 patients with grade 4 heart failure had albuminuria of grade 1. Seven of these 11 had albuminuria of grade 2, 3 had albuminuria of grade 3 and 1 had grade 4 albuminuria.

Volhard,[5] Ehrström[2, 3] and others have stated that the degree of albuminuria is not in proportion to the degree of cardiac insufficiency. Our data do not support this contention. There seemed to be a fairly positive correlation between the degree of heart failure and the degree of albuminuria.

A fairly close correlation was also found to exist between the grade of albuminuria and the group of hypertension as determined by funduscopic examination in the 21 hypertensive patients who had undergone funduscopic examination. Thus, in these patients, all who did not have albuminuria had group 1 hypertension. Among the patients with grade 1 albuminuria, none had hypertension graded higher than 2. Six of the 12 patients with grade 2 albuminuria had group 2 hypertension, and the other six of these 12 had hypertension of group 1 or group 3.

There was no correlation between the grades of albuminuria and the values for either systolic or diastolic blood pressure.

Among the 161 patients in group 1, 216 urinalyses were recorded, with 59 instances of hematuria. It was found that there was no consistent relationship between the grade of albuminuria and the grade of hematuria.

For 144 patients a total of 157 determinations of blood urea were done, and it was likewise found that no relationship existed between the value for blood urea and the grade of albuminuria.

Comment

Much experimental work has been done to elucidate the mechanisms in the production of

albuminuria. The following are brief references to some of these investigations.

Hayman and Bender[6] injected citrated plasma from three nephritic patients with heavy albuminuria into persons with normal kidneys. No albuminuria resulted in the healthy recipients. Rusznyák and Németh[7] perfused a dog's kidneys with Ringer's solution to which human blood from a patient with nephrosis had been added. No albumin appeared in the urine, but when they added sodium oleate to lower the surface tension, albumin did appear. Upon the addition of calcium chloride, the membrane no longer allowed albumin to pass through.

Richards[8] injected epinephrine intravenously into normal healthy rabbits in such a way that its action was maintained for several minutes. Transient albuminuria resulted. In healthy cats, subjected to stimuli which excited fear or rage, albuminuria subsequently developed. In like manner, Starr[9] conducted four groups of experiments. He gave epinephrine intravenously to rabbits and to anesthetized dogs, aroused cats to fright or anger, and injected ephedrine into men. In all these experiments the common renal feature of vasoconstriction was recorded. Transient albuminuria developed in each case.

Bolton[10, 11] achieved temporary complete constriction of the inferior vena cava by means of a ligature and temporary partial constriction by means of a snarelike device, the manipulation of which determined the changes in the caval pressure. He noted an albuminuria which disappeared rapidly after the resumption of normal circulation. He explained this finding by the remarkable degree of reversibility observed in the asphyxial changes in the mesenteric capillaries. Within limits, it appears that recovery to normal is almost complete; certainly it is entirely complete so far as permeability to protein is concerned. Apparently, therefore, the plasma proteins can pass through the temporarily asphyxiated capillary wall, although the same wall, under conditions of sufficient blood flow and ample oxygenation, will still retain its normal impermeability to proteins.

The consensus of these and most other investigators in this field is that the albuminuria probably is due to an increased capillary permeability of the glomeruli as a result of stagnation of blood and of anoxemia from the inefficient circulation through the kidneys, due to failure of the heart.

With reference to the quantitative values of albuminuria, the information in the literature is scanty. Most of the textbooks state that albuminuria in cardiac insufficiency is a fairly common phenomenon but that the protein content is rather small—less than 5 mg. per 100 ml. of urine. As mentioned earlier, grade 1 albuminuria in this study represented 5 to 20 mg. of albumin per 100 ml. of urine and a classification of grade 4 albuminuria required more than 100 mg. of albumin per 100 ml. of urine. Therefore, the degree of albuminuria discussed in this paper is relatively severe.

Summary

(1) Albuminuria may be an integral part of the picture of congestive heart failure. Of 161 patients in whom the histologic renal findings were considered to be either normal or to be of such a nature as not to be responsible in themselves for albuminuria and in whom clinically obvious causes for albuminuria had been eliminated (group 1 of this study), 141 or 88 per cent had albuminuria.

(2) The incidence of albuminuria was about equal among the various types of heart disease when heart failure existed.

(3) A trend existed for the grade of albuminuria to parallel the grade of heart failure.

(4) Based on a study of 21 patients, there seemed to be a correlation between the grade of albuminuria and the group of hypertension, according to funduscopic examination.

(5) No correlation was found between the grade of albuminuria on one hand and the systolic or diastolic values for blood pressure, the known duration of elevated blood pressure, the grades of hematuria or the values for blood urea on the other hand.

(6) Among the 161 patients with heart failure in our group 1, there was no predominant renal lesion associated with any one cardiac lesion.

Summario in Interlingua

Albuminuria pote esser un parte integral del syndrome de congestive disfallimento cardiac. Esseva investigate 161 patientes in qui le constatationes historenal poteva considerar se como normal o esseva de character a render impossibile considerar los como responsabile per se pro albuminuria. In omnes, obvie causas de albuminuria habeva essite eliminate. Sed 141 de illes (88 pro cento) habeva albuminuria. Le frequentia del albuminuria esseva distribuite plus o minus equalmente inter le varie typos de morbo cardiac, in tanto que disfallimento cardiac esseva involvite. Esseva notate le tendentia del grado del albuminuria a conducer se parallelmente al grado del disfallimento cardiac. Un studio de 21 patientes pareva indicar un correlation inter le grado del albuminuria e le gruppo de hypertension secundo le examine fundoscopic. Nulle correlation esseva constatate inter—de un latere—le grado del albuminuria e—del altere latere—le valores systolic o diastolic del pression sanguinee, le cognoscite duration del elevate pression sanguinee, le grado de hematuria, o le valores de urea sanguinee. Inter le 161 patientes hic reportate, nulle specific lesion renal esseva predominantemente associate con ulle specific lesion cardiac.

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Angiocardiographic Observations of Intracardiac Flow in the Normal and in Mitral Stenosis

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Intracardiac flow of intravenously injected radiopaque material was studied by means of rapid simultaneous biplane stereoscopic angiocardiography. Intracardiac circulation times thus determined may be found useful in recognizing structural abnormality and in detecting changes in cardiac function. In mitral stenosis, a distinctive, but not specific, pattern was recognized whether or not mitral valvotomy had been performed. No relationship was found between left atrial size and left atrial circulation time or between the degree of opacification of the left atrium and that of the left ventricle to differentiate "pure" mitral stenosis from mitral stenosis with regurgitation as diagnosed at the time of surgery or to predict the degree of mitral stenosis reported by the surgeon.

THE primary purpose of this communication is to describe the angiocardiographic characteristics of the intracardiac flow of radiopaque material in normal subjects and in those with mitral stenosis in those who had had mitral valvotomy and in those who had not. The specificity of the pattern of flow in mitral stenosis is evaluated together with a study of the modifications, if any, associated with differences in heart size, rhythm, myocardial function and medical or surgical therapy.

Methods and Materials

The biplane stereoscopic angiocardiographic apparatus devised by Chamberlain was employed.[1] The x-ray tube to film distance is 100 cm.

Fifty ml. of 70 per cent Urokon were injected as rapidly as possible, using a Robb-Steinberg syringe. Injection time was no longer than two seconds. Roentgenograms in the posterior-anterior and left lateral projections were obtained simultaneously, at an interval of 0.7 second, beginning with the instant of injection, for at least 21 seconds. Subsequent biplane roentgenograms were obtained at varying intervals depending upon clinical evaluation of heart function and roentgenographic determination of heart size. The posteroanterior and left lateral projections were chosen to identify with certainty portions of the cardiovascular silhouette, to minimize overlapping and to facilitate reproducibility in positioning of the subject. Identification of opacity within specific regions of the cardiovascular silhouette was further enhanced by stereoscopy.

Angiocardiograms were studied for time of appearance and disappearance of opacification in the superior vena cava, right heart, pulmonary artery, left atrium, left ventricle and aorta. The following "circulation times" were determined:

(1) *Superior vena cava time;* the duration of opacification of the superior vena cava.

(2) *Initial right heart time;* the time after initial superior vena cava visualization at which right atrial opacification is first visible.

(3) *Right heart time;* the duration of opacification of the right heart, measured from initial opacification of the right atrium to disappearance of contrast material from the right ventricle. (The disappearance of opacification of the right atrium and its beginning in the right ventricle could not be determined with certainty.)

(4) *Initial pulmonary artery time;* the time after initial right heart visualization at which the pulmonary artery first becomes opacified.

(5) *Pulmonary artery time;* the duration of opacification of the pulmonary artery and its major branches.

(6) *Initial left atrial time;* the interval between initial opacification of the right heart and the first visible opacification of the left atrium.

(7) *Left atrial time;* the duration of opacification of the left atrium.

(8) *Left ventricular time;* the duration of opacification of the left ventricle.

(9) *Interval between disappearance of opacification of the pulmonary artery and its appearance in the ascending aorta.*

(10) *Intracardiac circulation time;* the interval

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TABLE 1.—*Angiocardiographic Circulation Times and "Volume" of Left Atrium in Individuals without Cardiovascular Disease*

	Subject	Age	Sex	Diagnosis	Superior Vena Cava Time	Initial Right Heart Opacification	Right Heart Time	Initial Pulmonary Artery Opacification	Pulmonary Artery Time	Initial Left Atrial Opacification	Left Atrial Time	Initial LA Opac. to Initial LV. Opac.	Left Ventricular Time	End of P.A. Opac. to Initial Aortic Opac.	Intra cardiac Circulation Time	Left Atrial "Volume" (c.c.)	Remarks
1	C. B.	21	M	Epilepsy	3.5	0.7	5.6	0.7	5.6	4.9	5.6	1.4	4.2	0.6	6.3	?	Limits of left atrium not clearly defined on lateral projection.
2	M. W.	45	M	Duodenal ulcer	4.9	0	4.9	1.4	4.2	4.9	5.6	0.7	6.3	0.6	5.6	100	
3	J. C.	60	M	Bronchiogenic CA	2.8	0.7	4.2	0.7	4.9	4.9	1.4	0	5.6	0.6	5.6	?	Left atrium clearly defined on only two films.
4	J. S.	43	M	Left hilar mass ?	4.2	0.7	4.9	0.7	4.9	6.3	4.2	0	4.2	1.3	6.3	?	Left hilar prominence due to normal pulmonary artery. Limits of left atrium not clearly defined on anterior projection.

from initial opacification of the right atrium to initial opacification of the ascending aorta.

The circulation times thus determined are reported in terms of seconds and fractions thereof rather than in number of cardiac cycles. Actually, the heart rate varied from 100 per minute to 150 per minute with the mean at 120 per minute (1.4 cardiac cycles per exposure). The degree of opacification was determined by inspection and was graded 0 (no recognizable opacification) to 4 (maximal and intense opacification). Such determinations were corroborated by densitometer readings but this did not appear to be of additional value.

By using the beginning of opacification of the right heart, that is, the exposure in which contrast material is first visualized in the right atrium, as zero time, we have found that such determinations of circulation time are reproducible. All readings were done independently by at least two observers. With this method, repeated studies in the same patients, yielded similar results provided the superior vena cava time was identical.

The "volume" of the left atrium is represented, for purposes of this study, by the product of the greatest horizontal and vertical diameters of the opacified left atrium in the posteroanterior projection and its greatest horizontal diameter in the left lateral projection.

Eighty-one angiocardiograms were made of 67 subjects without heart disease or with various types of congenital or acquired heart disease. This report is based primarily on the findings in four individuals without cardiovascular disease, 22 with mitral stenosis and 31 with mitral stenosis and mitral valvotomy. Clinical details for each individual in the various groups appear in tables 1, 2 and 3, respectively.

RESULTS

Each angiocardiographic study consisted of a minimum of 68 exposures and many had more than 80. In each study, degree of opacification was plotted against time for each portion of the circulation studied, a method similar to the one used by Lind, Spencer and Wegelius.[2]

(1) *The Normal Angiocardiogram*

The intracardiac circulation time in four subjects without cardiovascular disease was not greater than 6.3 seconds and always exceeded the right heart time and pulmonary artery time. In three of the four subjects, the intracardiac circulation time also exceeded the left atrial time. In the remaining subject, the intracardiac and left atrial circulation times were each 5.6 seconds.

Initial right heart time occurred within 0.7 second of initial visualization of the superior vena cava. Initial pulmonary artery time was no longer than 1.4 seconds and initial left atrial time no longer than 6.3 seconds. The left atrial time varied from 4.2 to 5.6 seconds. In one case, the left atrium was identified with certainty in only two consecutive films.

The left atrial density was never great and

TABLE 2.—*Angiocardiographic Circulation Times and "Volume" of Left Atrium in Individuals with Rheumatic Heart Disease and Mitral Stenosis without Valvotomy*

	Subject	Age	Sex	Diagnosis	Superior Vena Cava Time		Initial Right Heart Opacification		Right Heart Time	Initial Pulmonary Artery Opacification		Pulmonary Artery Time	Initial Left Atrial Opacification		Left Atrial Time	Initial LA Opac. to Initial LV Opac.		Left Ventricular Time	End of PA Opac. to Initial Aortic Opac.	Intra Cardiac Circulation Time	Left Atrial "Volume" (c.c.)	Remarks
1	C. H.	50	F	NSR. SL. EH. °Dig.	4.2	0			7.7	0		9.1	5.6		14.0	2.1		9.8	−1.3	7.7	201	
2	M. G.	30	F	NSR. Pregnancy. °Dig.	3.5	0			4.9	0.7		5.6	4.9		6.3	0		9.1	0.6	6.3	216	
3	V. C.	31	F	NSR. °Dig.	7.0	0.7			7.0	1.4		6.3	6.3		9.8	2.1		7.7	0.6	7.7	260	
4	M. T.	39	F	NSR. Mod. EH. + DIG. Probably active RF.	5.6	0			19.6	1.4		18.2	9.8		9.8	7.0		2.8	−7.6	11.9	281	Left ventricle seen with certainty in only 4 films.
5	E. W.	46	F	AF.SL.EH. + Dig.	2.8	0			20.3	1.4		18.9	7.0		13.3	1.4		11.9	−13.2	9.8	303	Left atrial thrombosis. Puddling in rt. ventricle.
6	M. P.	62	F	AF.SL.EH. + Dig.	5.6	0			20.3	1.4		18.9	9.1		11.2	2.8		8.4	−11.1	9.8	304	Left atrial thrombosis. Puddling in rt. ventricle.
7	L. N.	45	F	AF.(T).SL.EH. + Dig.	5.6	0			7.7	0.7		9.8	6.3		14.0	2.1		11.9	−1.3	9.1	324	
8	C. W.	45	F	NSR. °Dig.	2.8	0			4.9	0.7		4.9	5.6		7.0	2.1		4.9	2.7	7.7	350	
9	L. S.	42	F	NSR. °Dig.	2.8	0			4.9	0.7		4.2	4.2		6.3	0.7		7.0	1.3	5.6	351	
10	G. S.	48	F	NSR. °Dig.	6.3	0.7			6.3	0.7		9.1	5.6		11.2	1.4		10.5	−2.0	7.0	352	
11	J. P.	22	F	NSR. °Dig.	4.2	0.7			5.6	0.7		5.6	4.9		7.0	1.4		4.9	0.6	6.3	357	
12	A. V.	31	M	NSR. °Dig.	3.5	0			5.6	0.7		5.6	6.3		6.3	0		7.7	1.3	6.3	423	
13	I. H.	35	F	NSR. °Dig.	3.5	0.7			4.9	0		5.6	4.9		7.0	0.7		6.3	−0.6	6.3	441	
14	R. D.	51	F	NSR. Mod. EH. + Dig.	4.9	0.7			4.9	0.7		4.2	4.9		7.0	0.7		7.0	1.3	5.6	442	
15	V. K.	49	F	AF. Mod. EH. + Dig.	7.7	0			22.4	1.4		21.0	9.8		12.6	1.4		11.2	−12.5	11.2	450	Puddling in right ventricle.
16	M. S.	35	F	NSR. Pregnancy. °Dig.	4.2	0.7			7.0	1.4		8.4	6.3		11.9	0.7		12.6	0.6	8.4	455	
17	B. L.	35	F	NSR.SL.EH. °Dig.	5.6	0.7			6.3	0		9.8	7.0		13.3	2.8		11.2	0	9.1	480	
18	M. W.	21	F	NSR.SL.EH. + Dig.	4.2	0.7			5.6	0		8.4	4.9		14.7	2.8		11.9	1.3	9.1	499	
19	A. M.	41	M	NSR.SL.EH. °Dig.	4.9	0.7			5.6	0.7		7.7	5.6		9.8	1.4		8.4	−2.0	6.3	520	
20	L. G.	50	F	AF. Mod. EH. + Dig.	4.2	0			10.5	1.4		9.1	8.4		11.9	2.1		9.8	−0.6	9.1	680	
21	G. S.	46	F	AF. Marked EH. + Dig.	3.5	0			14.7	0		13.3	9.1		7.0	?		?	−3.4	9.8	704	
22	L. S.	50	M	AF. Mod. EH. + Dig.	4.9	0.7			7.0	1.4		8.4	7.0		13.3	2.1		11.9	0	9.1	720	

+ Dig. = Digitalis received.
°Dig. = Digitalis not received.
NSR. = Normal sinus rhythm.
EH. = Enlarged heart.
RF. = Rheumatic fever.
AH. = Atrial fibrillation.

its maximum was recorded as grade 2. It was always less than that of either the right heart or the pulmonary artery. Indeed, the pulmonary veins adjacent to the left atrium were usually more clearly defined than the left atrium itself so that the globular appearance of this portion of the pulmonary veins resembled an accessory atrium. Left ventricular density was similar to that of the left atrium.

Because of the relatively poor definition of the borders of the left atrium in these subjects, measurement of the diameters of the left atrium was possible in only one instance. In this one instance, the "volume" of the left atrium was 100 cc. In the others, the left atrial borders could be determined with certainty in only one projection or not at all.

The angiocardiographic circulation times for the subjects without cardiovascular disease are given in table 1.

(2) *Mitral Stenosis without Mitral Valvotomy*

In the 22 individuals with mitral stenosis who did not undergo mitral valvotomy, the intracardiac circulation time varied from 5.6 to 11.9 seconds. While the intracardiac circulation time in individuals with mitral stenosis may exceed the maximum normal value of 6.3 seconds, it was never longer than 9.1 seconds in the absence of atrial fibrillation, cardiomegaly, localized "puddling" of the contrast substance in the right ventricle or heart failure. It exceeded 9.1 seconds in only 1 of 15 patients with sinus rhythm. This individual, with an intracardiac circulation time of 11.9 seconds, probably had active rheumatic myocarditis with moderate cardiac enlargement without overt failure. Of the others with sinus rhythm only two had an intracardiac circulation time as long as 9.1 seconds. On the other hand, all of the seven patients with atrial fibrillation had an intracardiac circulation time of 9.1 seconds or more. There was no unusual delay in initial opacification of the right heart. In 13 of the 22, the right heart time exceeded the maximum normal value of 5.6 seconds.

Prolongation of the right heart time is apparently related, at least in part, to the duration of opacification of the superior vena cava since 7 of the 13 cases with a prolonged right heart time had a superior vena cava time greater than 4.9 seconds. Of the remaining six, five had atrial fibrillation. Two of these five showed localized "puddling" of the contrast material in the right ventricle. Regardless of rhythm, an intracardiac circulation time in excess of 9.1 seconds also was associated with marked prolongation of the right heart time.

Initial pulmonary artery time was no more than 1.4 seconds as in the normal.

The pulmonary artery and its branches were always enlarged to varying degrees. Peripherally, there was either gradual tapering of the pulmonary branches or an abrupt decrease in calibre. In some, the distal branches appeared abundant while in others the distal branches were not opacified, particularly if the pulmonary artery and heart were markedly increased in size. In contrast to the normal, the pulmonary artery time frequently exceeded the right heart time when the latter was not markedly prolonged. Opacification of the pulmonary artery disappeared before initial aortic opacification in nine cases. Persistence of opacification in the pulmonary artery long after initial aortic opacification was always associated with a long right heart time.

Initial left atrial time was frequently more than 6.3 seconds. The degree of opacification of the left atrium increased quickly to a maximum of grade 4 and remained at that intensity for a variable period of time with terminal fading. In mitral stenosis, the shorter the left atrial time, the sharper the appearance and disappearance of opacification of the left atrium.

The shape of the opacified left atrium is ellipsoid with the long axis in the lateral projection and horizontal in the anterior projection. Its surface is smooth even at the entrance of the enlarged pulmonary veins. The left auricle was frequently opacified. In the anterior view, the left auricle projected from the left lateral and superior portion of the left atrium and frequently reached the left border of the cardiac silhouette. In the lateral projection, the left auricular density was superimposed anteriorly and superiorly upon the atrial density. In the presence of left auricular thrombosis, the left auricle was not opacified and the border between the opacified left atrium and its appendage was irregular.

The borders of the left atrium were readily

TABLE 3.—*Angiocardiographic Circulation Times, "Volume" of Left Atrium and Findings at Operation in Individuals with Mitral Stenosis after Valvotomy*

	Subject	Age	Sex	Diagnosis	Superior Vena Cava Time	Initial Right Heart Opacification	Right Heart Time	Initial Pulmonary Artery Opacification	Pulmonary Artery Time	Initial Left Atrial Opacification	Left Atrial Time	Initial L.A. Opacification to Initial L.V. Opacification	Left Ventricular Time	End of P.A. Opacification to Initial Aortic Opac.	Intracardiac Circulation Time	Left Atrial "Volume" (c.c.)	Size of Mitral Orifice		Regurgitant Jet		Calcification	Time of Study Post-Op. Remarks
																	Pre-Op	Post-Op	Pre-Op	Post-Op		
1	L. M.	43	F	NSR. + Dig.	7.0	0	8.4	1.4	9.1	7.7	7.0	1.4	5.6	−2.0	8.4	241	Tip	1½ F.	+	+	+	Dye in superior vena cava faintly visible throughout study. 15 mo.
2	M. G.	56	F	AF. Mod. EH. + Dig.	5.6	0.7	15.4	0.7	15.4	9.8	32.9	2.1	30.8	−1.3	13.3	280	Tip	1½ F.	0	+	+	Puddling in right ventricle. 4 mo.
3	T. H.	32	F	NSR.SL.EH. °Dig.	4.2	0	11.9	0.7	12.6	6.3	14.0	2.1	11.9	−4.8	8.4	287	7 x 2 mm.	21 x 21 mm.	0	0	0	Dye in anterior thoracic veins. 5 mo.
4	C. P.	28	F	NSR.SL.EH + Dig.	7.7	0.7	7.0	0.7	7.7	4.9	11.9	2.1	7.7	−1.3	7.0	304	String like bands	Split	0	0	0	Dye in right innominate vein. 20 mo.
5	J. P.	22	F	NSR. + Dig.	4.2	0	7.0	0.7	4.9	4.2	6.3	1.4	4.9	0.6	5.6	324	2-3 mm.	1½-2 cm.	0	0	0	13 days
6	D. C.	38	M	AF.SL.EH. + Dig.	4.2	0	7.0	1.4	8.4	7.7	11.2	2.1	9.1	0	9.1	324	Tip	2 F.	0	+	+	36 mo.
7	F. K.	42	F	AF.SL.EH. + Dig.	4.2	0.7	5.6	0.7	6.3	4.2	10.5	2.1	8.4	0.6	7.0	327	1 Match	Opened	0	0	0	28 mo.
8	F. P.	30	M	NSR. °Dig.	2.8	0	4.2	0.7	3.5	4.2	4.2	0.7	3.5	2.0	5.6	330	Several mm.	1½ F.	+	+	+	12 mo.
9	M. W.	39	F	NSR. + Dig.	4.2	0.7	4.2	0.7	4.9	4.9	8.4	2.1	4.9	−0.6	4.9	331	6 x 2 mm.	22 x 22 mm.	0	0	0	15 mo.
10	M. C.	36	F	NSR. + Dig.	4.2	0	6.3	0.7	9.1	7.0	22.4	2.1	10.5	−0.6	8.4	?	Cigarette	2½ F.	0	+	+	7 mo. P-A only
11	F. D.	35	F	NSR. Mod. EH. + Dig.	4.9	0.7	4.9	0.7	5.6	4.9	7.0	2.1	4.2	1.3	7.0	342	2 Match	2 F.	0	0	0	29 Mo.
12	E. P.	30	F	NSR. Mod. EH. + Dig.	3.5	0	7.0	0.7	7.7	6.3	8.4	1.4	7.7	0	7.7	?	3 Match	2 F.	0	+	0	27 Mo. Lateral only
13	A. V.	31	M	NSR. + Dig.	3.5	0	4.9	0.7	4.9	4.9	6.3	1.4	4.9	1.3	6.3	374	Minimal stenosis	Minimal stenosis	+	+	+	22 Days
14	E. H.	42	F	AF. Mod. EH. + Dig.	2.8	0.7	6.3	0.7	7.0	5.6	14.0	5.6	7.0	1.3	8.4	420	Cigarette	2 F.	+	+	+	18 Mo.
15	E. S.	41	M	NSR. Mod. EH. °Dig.	3.5	0	5.6	0.7	9.1	7.0	22.6	?	?	1.3	10.5	455	<1 cm.	>1.5 cm.	0	0	+	9 mo. L.V. not visualized
16	A. M.	41	M	AF.SL.EH. + Dig.	7.0	0	15.4	1.4	11.2	6.3	10.5	0.7	9.8	−4.8	7.7	455	Tip	Enlarged	0	0	0	10 Days
17	L. N.	45	F	AF.SL.EH. + Dig.	6.3	0	9.8	1.4	7.0	5.6	12.6	2.1	7.7	0	7.7	465	Tip	Enlarged	0	0	0	20 Days
18	R. L.	29	F	NSR.SL.EH. + Dig.	3.5	0	7.0	1.4	6.3	7.7	11.2	1.4	8.4	3.4	10.5	510	2 x 12 mm.	24 x 24 mm.	0	0	0	16 Mo.
19	D. W.	28	F	NSR. Mod. EH. °Dig.	2.8	0	4.2	0.7	5.6	5.6	7.0	0.7	14.0	0.6	6.3	540	12 x 3 mm.	1½ F.	0	+	+	19 Mo.

20	M. I.	26	F	NSR.SL.EH. °Dig.	2.8	0	4.9	0	6.3	6.3	9.1	2.8	6.3	2.7	8.4	546	5 mm.	1½ F.	0	0	0	10 Mo.
21	L. C.	38	M	AF. Mod. EH. + Dig.	4.2	0	5.6	0.7	7.7	6.3	10.5	2.1	7.0	0.6	8.4	588	20 x 6 mm.	Larger	+	++	+	7 Mo.
22	R. D.	27	M	NSR. Mod. EH. + Dig.	7.7	0	12.6	1.4	14.7	9.1	20.5	1.4	29.1	−1.3	14.7	591	22 x 1 mm.	25 x 25 mm.	+	++	+	15 Mo.
23	G. D.	49	M	AF. Marked EH. + Dig.	7.0	0.7	14.7	1.4	13.3	11.9	23.8	?	?	−11.2	24.5	595	20 x 2 mm.	22 x 22 mm.	+	+	+	14 Mo. L.V. not visualized
24	S. N.	36	F	NSR.SL.EH. + Dig.	4.2	0	6.3	0.7	8.4	7.7	11.9	?	?	0.6	9.1	606	Tip	1½ F.	0	+	0	27 Mo. L.V. not visualized
25	G. S.	46	F	AF. Marked EH. + Dig.	18.9	0	20.3	2.1	20.3	9.8	10.5	?	?	−8.3	11.9	700	1 F.	1½ F.	+	+	0	11 Days L.V. not visualized
26	A. S.	43	F	AF. Marked EH. + Dig.	5.6	0	15.4	2.1	14.0	14.7	66.5	?	?	10.4	17.5	700	1 F.	1½ F.	+	+	+	23 Mo. L.V. not visualized
27	I. S.	49	M	AF. Mod. EH. + Dig.	7.0	0	8.4	2.1	7.0	7.0	12.6	1.4	11.2	0.6	9.1	765	Tip	1½ F.	0	+	+	11 Mo. Increased extracardiac density
28	R. W.	41	F	AF. Marked EH. + Dig.	9.8	0	14.0	0.7	12.6	9.1	23.1	4.9	7.7	1.3	14.0	863	6 x 2 mm.	28 x 28 mm.	0	0	+	Dye in subclav. vein. 12 mo.
29	M. E.	43	F	AF. Marked EH. + Dig.	10.5	0	19.6	2.8	16.8	16.1	35.0	?	?	9.8	29.4	870	1 x 1½ cm.	2.5 cm.	0	0	+	24 Mo. L.V. not visualized
30	E. M.	33	M	AF. Mod. EH. + Dig.	7.7	1.4	13.3	2.1	9.1	11.2	18.2	?	?	5.5	16.8	Huge	Minimal stenosis	Minimal stenosis	++	++	+	35 Mo. L.V. not visualized. Giant left atrium lateral only
31	H. H.	50	F	AF. Marked EH. + Dig.	6.3	0	51.1	2.1	28.7	12.6	29.4	?	?	10.4	41.3	1205	1 F.	1½ F.	+	+	+	11 Mo. L.V. not visualized

delineated so that the diameters were easily measured. In the entire group, the "volume" of the left atrium varied from 201 cc. to 720 cc. The volume of the left atrium did not change appreciably during the cardiac cycle. Left atrial volume in excess of 400 cc. was usually but not always associated with generalized cardiac enlargement. However, enlargement of the left atrium was not always proportional to that of the heart as a whole.

Atrial fibrillation was more common with larger left atria. The smallest left atrial "volume" in the presence of atrial fibrillation was 303 cc. in an individual with left atrial thrombosis. The other individual with left atrial thrombosis had a left atrial volume of 304 cc. Left atrial thrombosis was recognized by the filling defects in the left atrium and confirmed in the one who later had mitral valvotomy.

Change in size of the left atrium was not related to age. The four largest atria were observed in individuals 41 years of age or older and the smallest occurred in a 50 year old woman with mitral stenosis and paroxysms of pulmonary edema for at least 20 years.

The left atrial time varied from 6.3 to 14.7 seconds. The left atrial time always exceeded the right heart time and pulmonary artery time if the right heart time was not markedly prolonged. No linear relationship was observed between left atrial volume and left atrial time.

Initial left ventricular time was frequently greater than 1.4 seconds. The longest such time in the normal was 1.4 seconds. In one case, this time was 7 seconds and the contrast substance in the left ventricle was barely visible. In another, nonvisualization of the left ventricle prevented determination of this time.

The degree of opacification of the left ventricle generally was slight compared with that of the left atrium. Frequently, opacity within the left ventricle was seen only as a small area at the site of origin of the ascending aorta and then sometimes in only one projection, particularly the lateral. In no instance did opacification of the left ventricle remain constant in degree throughout the study. Rather, there was variation in density, often considerable, from one film to another. During diastole, the left ventricle may be markedly opacified. When grade 4 opacification was noted, it was not long sustained. In general, the smaller the left atrium, the better the degree of opacification of the left ventricle. However, the larger the left atrium the longer the left ventricular time.

The angiocardiographic circulation times in this group are given in table 2.

(3) *Mitral Stenosis with Mitral Valvotomy*

In the 31 individuals with mitral stenosis studied after mitral valvotomy, the intracardiac circulation time varied from 4.9 to 41.3 seconds. It exceeded 9.1 seconds in 3 of the 16 with sinus rhythm. One of these three had failure at the time of study. The other two had failure in the recent past. Of the 15 with atrial fibrillation, the intracardiac circulation time exceeded 9.1 seconds in eight. None had overt failure at the time of study. All of the 14 with an intracardiac circulation time of 9.1 seconds or more had right heart times that exceeded 5.6 seconds with one exception. This one patient, with moderate cardiac enlargement, had an unusually prolonged left atrial time and no visualization of the left ventricle. Initial right heart time was delayed to 1.4 seconds in one instance. This one had a huge left atrium that compressed and displaced to the right and anteriorly the superior vena cava, right heart and pulmonary artery.

The right heart time exceeded the normal 5.6 seconds in 22 of the 31 patients. Almost all of the individuals who had a markedly prolonged right heart time had atrial fibrillation.

The appearance of the pulmonary artery and its branches was similar to that seen in individuals without mitral valvotomy.

The degree of opacification and the contour of the left atrium were also similar to those in the individual without mitral valvotomy. Of course, the left atrium was not seen if it had been obliterated by surgery. The "volume" of the left atrium varied from 241 cc. to 1205 cc. In three instances the volume could not be determined because, for technical reasons, only one projection was obtained. Again, the larger volume occurred more frequently with atrial fibrillation and generalized cardiac enlargement. There was no relation between the "volume" of the left atrium and the size of the mitral orifice as reported by the surgeon

either before or after mitral valvotomy. The surgical finding of a regurgitant jet was apt to be associated with an enlarged left atrium. Appreciable variation in size of the left atrium during the cardiac cycle rarely occurred. It was occasionally seen only when the left atrium was not markedly enlarged and when clinical features of mitral regurgitation were present.

The "volume" of the left atrium and the surgical findings in this group of cases are presented in table 3.

The left atrial time varied from 4.2 to 66.5 seconds. In 22 of the 31 individuals who were subjected to surgery and in 14 of 22 who had not undergone surgery, it exceeded 9.8 seconds. When the right heart time was not prolonged, the left atrial time was never shorter than the pulmonary artery time or right heart time. One individual who had mitral valvotomy apparently for syncope was studied by us postoperatively. In him, the left atrial time and right heart time were each 4.2 seconds.

Initial left ventricle time was usually longer than 1.4 seconds. In eight cases nonvisualization of the left ventricle prevented determination of this time.

The left ventricle was not opacified in 7 of 9 cases with a left atrial "volume" of 595 cc. or more. In the remaining two, it was poorly visualized. In the others, the left ventricular opacification was slight compared with that of the left atrium. In three, left ventricular opacification was considerably greater than that ordinarily seen in mitral stenosis and in many films was equal to the density of the left atrium. Two of these three had regurgitant jets and the other, a loud systolic mitral murmur that appeared after surgery. Otherwise, we could not distinguish from the degree of left ventricular opacification those patients reported by the surgeon to have a regurgitant jet from those who did not have it.

The angiocardiographic circulation times in this group are presented in table 3.

Discussion

The intracardiac circulation time in this study is defined as the shortest time required for contrast material in detectable concentrations to travel from the right atrium to the ascending aorta. The time of initial opacification of the right atrium was taken as zero time rather than that of the superior vena cava as used by Figley[3] to allow for comparison and because it is the actual onset of intracardiac circulation.

In the normal the intracardiac circulation time exceeded the right heart time. The right heart, pulmonary artery and left atrial times were approximately equal in the normal and were no longer than 5.6 seconds. Opacification of the pulmonary artery disappeared before visualization of the ascending aorta was noted, confirming the observation of Figley.[3] Left atrial density was never great and was usually less than that of the right heart. The borders of the left atrium were poorly defined with the adjacent pulmonary veins usually better visualized.

In our study the intracardiac circulation time in individuals without cardiovascular disease did not exceed 6.3 seconds. The findings in patients with mitral stenosis are in marked contrast to those found in normal subjects. In the presence of mitral stenosis, the intracardiac circulation time may be prolonged However, it did not exceed 9.1 seconds in the absence of atrial fibrillation, "puddling" of contrast material in the right heart, marked cardiomegaly or heart failure.

No individual with an intracardiac circulation time less than 10.5 seconds exhibited clinical evidence of heart failure. With overt failure, the intracardiac circulation time was longer than 10.5 seconds. Moreover, in every instance in which the intracardiac circulation time was 10.5 seconds or longer, institution or intensification of an appropriate medical regimen resulted in a marked shortening of the circulation time, a finding that suggests the possibility of previously existing subclinical heart failure.

The pulmonary artery time may be much longer than the right heart time and the pulmonary artery may remain visualized after initial aortic opacification. Initial left atrial time was usually longer than in persons with normal hearts. In the absence of a prolonged right heart time, the left atrial time was almost always longer than 6.3 seconds and exceeded the right heart time and pulmonary artery time.

To determine the "volume" of the left atrium, the product of the greatest horizontal and vertical diameters in the anterior projection and the greatest horizontal diameter in the lateral projection was used. This method was chosen because of difficulty in defining the left atrium as a constant geometric structure regardless of the presence or absence of heart disease. Rather than employing a theoretic constant, we use the three diameters alone. The product of these diameters does not represent the actual volume. Nevertheless, it provides a basis for comparison. In order to compare the volume thus obtained with that of the cardiac volume determined by Rohrer's method, the factor 0.63 should be used.[5] Accordingly, a measured "volume" of 100 cc. in normal hearts becomes 63 cc. Of course, this does not include the distortion factor of a tube-to-film distance of 100 cm. which would further decrease the measured "volume". This computed volume of the normal left atrium approximates that derived by postmortem study.[1] All cases but two with left atrial "volume" in excess of 400 cubic centimeters exhibited some degree of generalized cardiac enlargement. In general, the larger the left atrial "volume" the larger the heart. However, a small left atrial "volume" was sometimes observed in the presence of cardiomegaly and conversely large left atrial "volume" occasionally occurred with only a slight increase in heart size or even in instances in which, from conventional films, the heart was regarded as normal in size and configuration.

In mitral stenosis, the left atrium was not only increased in size from twice to as much as 12 times that seen in persons with normal hearts, but it was also intensely opacified and its borders were sharply defined. The increase in size of the left atrium in mitral stenosis is a constant finding and, as emphasized by Grishman, Sussman and Steinberg,[6] is the most important factor in the production of "mitralization" of the cardiac silhouette. The left atrium itself does not reach the left border of the cardiac silhouette. This border is straight or exhibits a convexity directed outwards due to prominence of the enlarged pulmonary artery, displaced to the left and anteriorly by the large left atrium. The left atrium, on the other hand, is also enlarged and frequently extends to the left border in the region of the left third segment. In the angiocardiogram, the left auricle may not be easy to recognize because it may be obscured in the anterior projection by the superimposed pulmonary vessels and, in the lateral projection, it is superimposed upon the anterior and superior portion of the left atrial density.

Increase in size of the left atrium was frequently observed in association with atrial fibrillation. Moreover, with comparable atrial volume and cardiac size, in the presence of atrial fibrillation, all of the circulation times tend to be longer than in those with sinus rhythm. The impairment of the circulation by atrial fibrillation has been demonstrated by Hansen, McClenden and Kinsman.[7] They observed a significant rise in cardiac output and a decrease in pulmonary blood volume upon conversion of atrial fibrillation to sinus rhythm.

In mitral stenosis, there may be a delay in opacification of the left ventricle following initial opacification of the left atrium. Moreover, opacification of the left ventricle is slight compared with that of the left atrium, as is illustrated in figure 1.

Intense and persistent opacification of the enlarged left atrium and slight or no opacification of the left ventricle are the angiocardiographic criteria for the diagnosis of mitral stenosis, an observation emphasized by Zinsser and Johnson.[8] If mitral regurgitation alone (diagnosed clinically by a loud mitral systolic murmur with radiographic evidence of left ventricular enlargement) was present, homogeneous opacification of the left atrium blending with that of the thick-walled left ventricle was found; this statement was true provided the left atrium did not show marked disproportionate enlargement compared with that of the left ventricle. Otherwise, no relationship could be found between the left atrial time and left atrial size, or between left atrial and left ventricular opacification, that would permit one to differentiate "pure" mitral stenosis, as diagnosed at the time of surgery, from surgically diagnosed mitral stenosis with regurgitation.

The finding in mitral stenosis of a left atrial time longer than the intracardiac circulation time and longer than the pulmonary artery

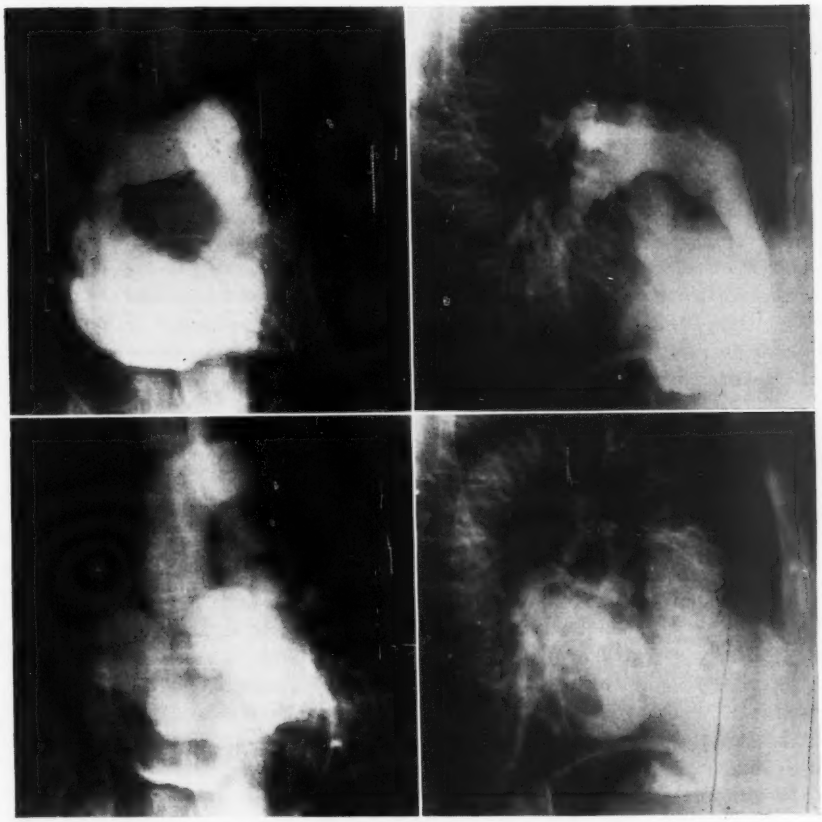

FIG. 1. Angiocardiograms demonstrating "puddling" of contrast substance in the right ventricle and filling defects in the left atrium and an obliterated left auricle due to thrombi. Case M. P., a 62 year old woman with mitral stenosis, atrial fibrillation and thromboembolism. The anterior projection is on the left and the lateral on the right. Time after initial opacification of the right atrium is 2.8 seconds in the upper pair and 14.0 seconds in the lower pair. Note the puddle of contrast substance in the inferior and posterior part of the right ventricle. Also note the filling defects in the central and posterior portion of the left atrium and the oblique entrance of the right inferior pulmonary vein. The left atrium is not opacified. The left atrium is irregularly marginated at its junction with the left auricle.

time suggests the existence of a block at the mitral valve. However, no relationship was found between left atrial "volume", left atrial time and the surgically reported size of the mitral orifice. Furthermore, we have found no correlation between these parameters, (left atrial "volume" and left atrial time) with either the age of the patient or the known duration of the rheumatic state. These findings, therefore, fail to support the concept dominant today that left atrial changes are proportional to the degree of narrowing of the mitral orifice and the duration of the obstruction. Such a lack of correlation has been found by others[9] and was the dominant clinical and pathological concept before the present surgical era. Indeed, our study shows no correlation between left atrial time or "volume" and right ventricular time, suggesting that the left atrial changes are not the immediate cause of right ventricular alteration. This independence suggests rather that the extent of myocardial disease, as suggested by almost all pathologic studies, is the primary determinant of these changes. Moreover, although correlation was poor with any parameter, the angiocardio-

graphic circulation times appear to correlate best with right ventricular time and secondly with left atrial "volume"; correlation was poorest with the surgically reported size of the mitral orifice. This finding is additional evidence suggesting that right ventricular function may be a very important factor determining the angiocardiographic circulation times. The myocardial factor is clinically demonstrated by the effect of medical treatment for myocardial dysfunction.

It is possible that prolongation of left atrial time may have no relationship at all to the obstruction produced by mitral stenosis. This is suggested by the fact that a prolonged left atrial time, with slight or no opacification of the left ventricle, may be seen in mitral stenosis with regurgitation or even in pure mitral regurgitation as diagnosed by the surgeon. A giant left atrium with marked regurgitation and minimal stenosis likewise gives the angiocardiographic pattern of intense opacification of the left atrium with delay in opacification or nonvisualization of the left ventricle. In an individual with mitral stenosis and surgically produced mitral regurgitation, cinefluorographic angiocardiography (32 frames per second on 16 mm. motion picture film with the aid of a fluoroscopic image amplifier) showed intense and persistent opacification of the left atrium and a marked delay in the beginning of opacification of the left ventricle.[10, 11] Opacification of the left ventricle was slight and was limited to the area immediately distal to the mitral valve.

Zinsser and Johnson, in explanation of the angiocardiographic finding of a pattern typical for mitral stenosis in those with additional mitral regurgitation, clinical or surgical or both, invoked the concept of "functional stenosis."[8] This hypothesis assumes, on the basis of clinical improvement after surgery, that the major indication of obstruction, and hence operability for its relief, is the angiocardiographic pattern characteristic for mitral stenosis and not the anatomic size of the mitral orifice and notwithstanding the surgical findings of a regurgitant jet. However, they did not attempt to prove their hypothesis by repeating the angiocardiographic study after surgery.

As stated previously, we agree with them that there is no relation between anatomic size of the mitral orifice and degree of left atrial enlargement or the duration of left atrial opacification. We disagree with them in their explanation of these findings and their evaluation of the significance of differences in opacification between the left atrium and the left ventricle.

The angiocardiographic technic does not permit measurement of actual flow but rather of intensity and time of visibility of opacification of cardiac chambers and great vessels. Assuming that technique is kept constant for each individual study, opacification depends upon concentration of contrast material in blood, depth of chamber or vessel in a given projection, and degree of blurring of contours due to motion during the exposure. (The latter factor varies with the phase of the cardiac cycle.) A further factor which is difficult to evaluate is that of streamline flow which may be particularly important in an enlarged chamber with a large residual volume of blood, such as the enlarged left atrium. In such a case, mixing of the contrast material with blood in the peripheral portions of the enlarged chamber may occur rather slowly. Subsequently, the inflowing blood with a higher concentration of contrast material may flow directly to the chamber's exit. Such an occurrence may be difficult or impossible to appreciate, even in biplane angiocardiographic studies.

Moreover, with a given concentration of contrast material, the greater the depth or thickness of the chamber, the greater will be the x-ray absorption or opacification, up to a maximum. In other words, for equal concentrations of contrast material, a larger chamber will appear more opaque than a smaller one. On the other hand, with the same quantity of contrast agent injected, the larger the chamber, the less the concentration of contrast material. Obviously, these two factors operate in opposite directions.

The left atrium, if it is enlarged, will always be considerably opacified, although not necessarily maximally, and regardless of stasis in the right ventricle because relatively small concentrations of contrast substance are effec-

tive due to the increased depth of the chamber. For this reason, the left atrial time will tend to be longer in those with a prolonged right heart time since the flow of opacified blood into the left atrium is continued over an abnormally long period. Actually, the left atrial time exceeded 8.4 seconds in 6 of 18 cases with a right heart time of 5.6 seconds or less and in 31 of 36 with a right heart time greater than 5.6 seconds.

In the enlarged left atrium, additional dilution occurs, at least initially. As the opacified blood leaves the left atrium, the contrast will be less concentrated the larger the atrium and thus its visualization in the left ventricle may be delayed since it is further diluted in this chamber initially. Again, dilution in the left ventricle depends upon the volume of residual blood in the left ventricle. By the above reasoning, it seems to follow that, regardless of the presence or absence of mitral stenosis, the larger the left atrium, the less will be the chance for visualization of the left ventricle.

These technical considerations appear to be equally applicable to the pulmonary arterial tree where the angiocardiographic finding of so-called "spasm of the distal pulmonary artery branches" has been reported. The larger the heart and the pulmonary artery, the more dilute will be the contrast material by the time it reaches the distal branches and the less likely it will be that these peripheral branches will be visualized. Such findings in themselves do not necessarily indicate the presence of pulmonary hypertension as has been suggested by Goodwin, Steiner and Lowe.[12] Indeed, in the present study, lack of opacification of the distal pulmonary vessels is correlated with increase in cardiac and pulmonary volume. On the other hand, in the individual with mitral stenosis and relatively normal-sized cardiac chambers and pulmonary artery, the distal vessels are opacified and more abundant and larger than those seen in the normal. Davies and co-workers[13] suggest that selective pulmonary arteriography may overcome some of the disadvantages of venous angiocardiography in the demonstration of these changes in the distal pulmonary arteries. However, with this procedure, the problem of dilution in the enlarged pulmonary artery and its branches remains and may even be increased because the total amount of contrast agent injected is decreased while injection is usually prolonged. Both factors would tend to impair opacification in distal pulmonary vessels.

The importance of depth of opacified chamber in visualization makes biplane angiocardiography mandatory if errors are to be avoided. The enlarged contrast-filled left atrium has a depth sufficient for easy visualization in any projection. The chamber is best visualized in lateral projection where its greatest depth is presented. In the case of the left ventricle, there may be appreciable differences in opacification in one projection compared with simultaneous exposures in another due to differences in cavity depth in various projections. Such differences depend upon the position of the heart, enlargement of the ventricle and the location and degree of obliquity of the septum. Unpredictably, the left ventricle may be better visualized in the anterior than in the lateral projection and vice versa (fig. 2). Moreover, there are marked systolic-diastolic differences in left ventricular opacification, in contradistinction to a practically constant degree of left atrial opacification regardless of the phase of contraction (fig. 3). This emphasizes the fact that the difference between left atrial and left ventricular opacification depends not only upon the circulation times and the degree of chamber enlargement, but also upon the phase of the cardiac cycle in which the roentgenogram is exposed. In mitral stenosis the left atrium undergoes relatively little cyclic change in size or degree of opacification, in marked contrast to the left ventricle which almost completely empties itself in systole unless failure is present. It is possible to secure a series of roentgenograms without visualizing the left ventricle in diastole. Conversely, ventricular diastole may be visualized several times. It is, therefore, important to have a simultaneous record of cardiac events and of each exposure, or to have angiocardiograms exposed in very rapid sequence. Finally, stereoscopy makes possible differentiation of extracardiac densities that may appear to be within the heart on a single projection. Stereos-

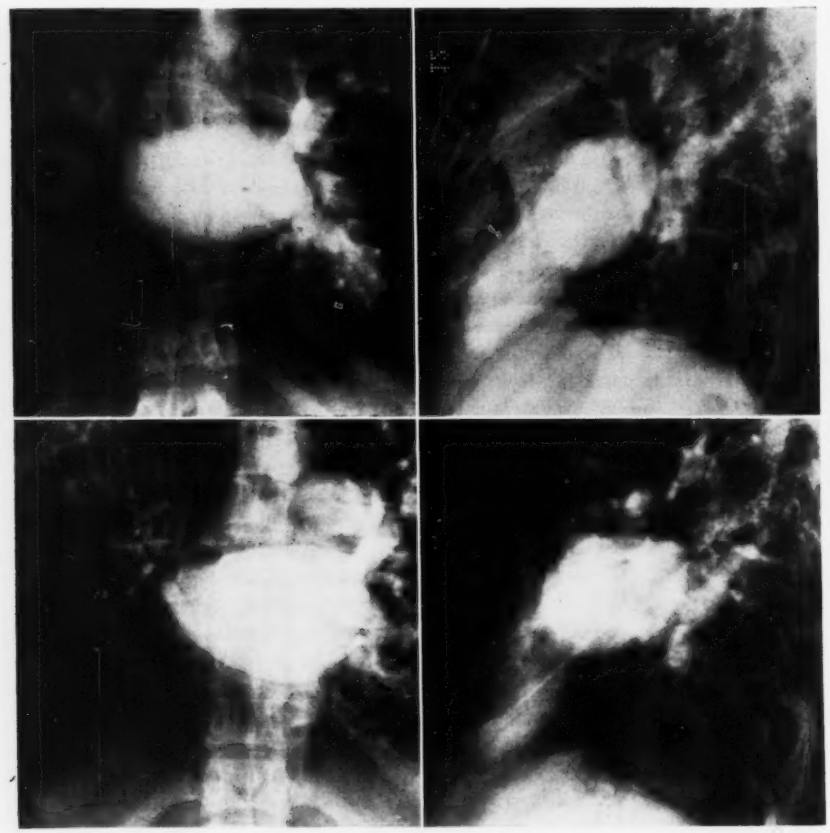

FIG. 2. Angiocardiograms in mitral stenosis before and after surgery demonstrating opacification of the left ventricle clearly on the lateral projection and poorly on the anterior projection. Case J. P., a 22 year old woman with mitral stenosis and sinus rhythm. The upper pair was taken 14 days before surgery and the lower pair 13 days after surgery. Both before and after operation time after initial opacification of the right atrium is identical. There was no regurgitant jet before or after surgery.

copy is particularly important in differentiating the left atrium from the pulmonary veins that converge on it.

The recognition that the "mitral" angiocardiographic pattern described may be independent of mitral stenosis is important if serious errors are to be avoided. Indeed, this pattern may be seen in the total absence of mitral valve disease. A 39 year old woman was admitted to the hospital in right heart failure. A diagnosis of mitral stenosis had been made and she was being prepared for mitral valvotomy. Because of the absence of a characteristic history of rheumatic fever and the absence of typical auscultatory features of mitral stenosis, a diagnosis was entertained of idiopathic right heart failure possibly of pulmonary origin. The angiocardiogram showed a pattern assumed to be typical for mitral stenosis. The left atrium remained opacified for 48.3 seconds and the left ventricle was never visualized. She died three weeks later of intractable right heart failure. Autopsy revealed no evidence of valvular disease. There was far advanced pulmonary artery disease and death was due to pulmonary infarction. Thus, enlargement of the left atrium, unassociated with valvular de-

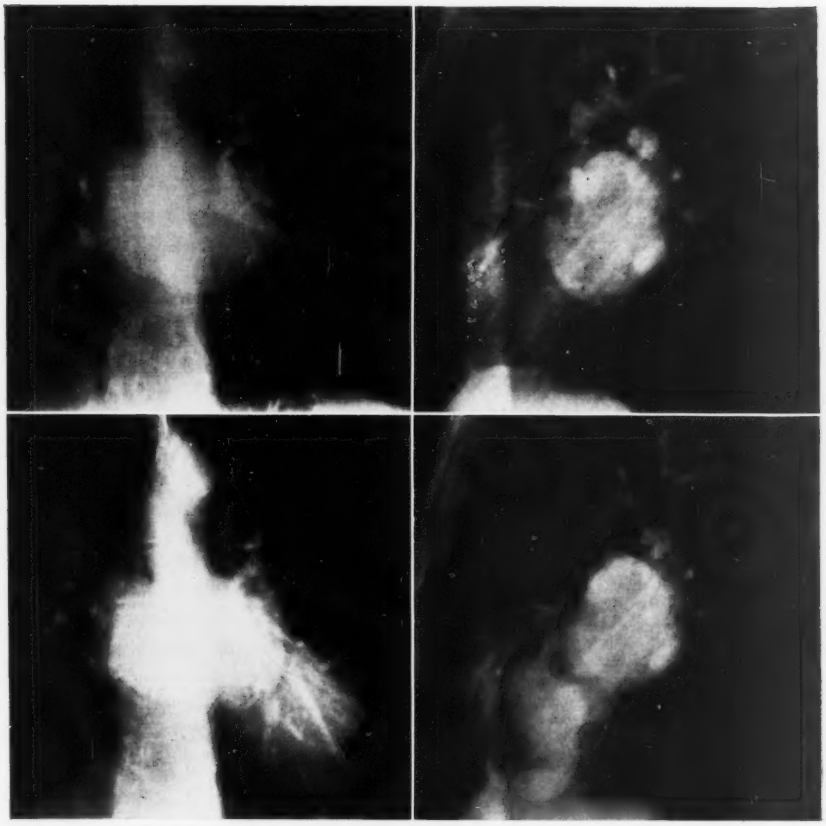

FIG. 3. Angiocardiograms demonstrating intense opacification of the left atrium and slight opacification of the left ventricle in mitral stenosis and also variability of opacification of left ventricle with phase of cardiac cycle. Case M. W., a 40 year old woman with mitral stenosis and sinus rhythm, 15 months after valvotomy. No regurgitant jet was present before or after surgery. A mitral systolic murmur appeared after surgery. The upper pair was taken at 6.3 seconds during ventricular systole and the lower pair at 7.7 seconds during ventricular diastole. Left ventricular opacification that is barely visible during systole is marked and intense during diastole. The left atrium is larger during ventricular systole and smaller during ventricular diastole.

formity, may produce the pattern of mitral stenosis.

However, the possibility of occult left ventricular failure in this instance could not be excluded, because it is easy to show that left ventricular failure of any origin, be it aortic valve disease, systemic hypertension or coronary artery disease, may produce angiocardiographic findings similar to those due to mitral valve disease. Figure 4 shows the angiocardiographic results in a group of individuals with disease of the aorta or left ventricle or both As in mitral stenosis, intensity of opacification of the left atrium or its duration is greatly increased. The distinction between these angiocardiograms and those due to mitral disease is, however, easy, because of the great thickness of the left ventricular wall, increase in degree and duration of the left ventricular opacification and, with aortic disease, frequent eccentric opacification of the aortic orifice. Additional mitral stenosis, however, if present, would be difficult if not impossible to detect by angiocardiography.

It is clear, therefore, that angiocardiography, in common with other technics, is not specific

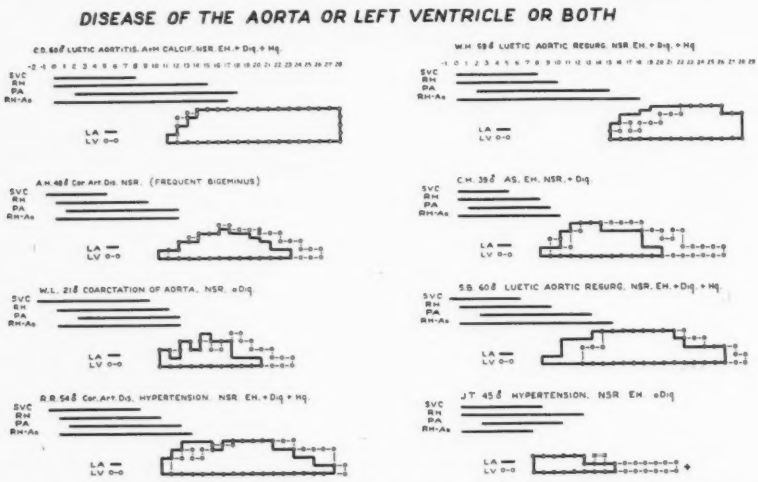
DISEASE OF THE AORTA OR LEFT VENTRICLE OR BOTH
C.D. 60♂ LUETIC AORTITIS. AHM CALCIF. NSR. EH. + Diq. + Hq.
W.H. 58♂ LUETIC AORTIC REGURG. NSR. EH. + Diq. + Hq
A.H. 48♂ Cor. Art. Dis. NSR. (FREQUENT BIGEMINUS)
C.H. 39♂ AS. EH. NSR. + Diq.
W.L. 21♂ COARCTATION OF AORTA. NSR. ±Diq
S.B. 60♂ LUETIC AORTIC REGURG. NSR. EH. + Diq. + Hq.
R.R. 54♂ Cor. Art. Dis. HYPERTENSION. NSR. EH. + Diq + Hq.
J.T. 45♂ HYPERTENSION. NSR. EH. ±Diq
SVC
RH
PA
RH-Ao
LA
LV

FIG. 4. Angiocardiographic results in individuals with disease of the aorta or left ventricle or both. Note in those with long intracardiac circulation times, the prolonged right heart time. Note also in many instances the intense and persistent degree of opacification of the left atrium.

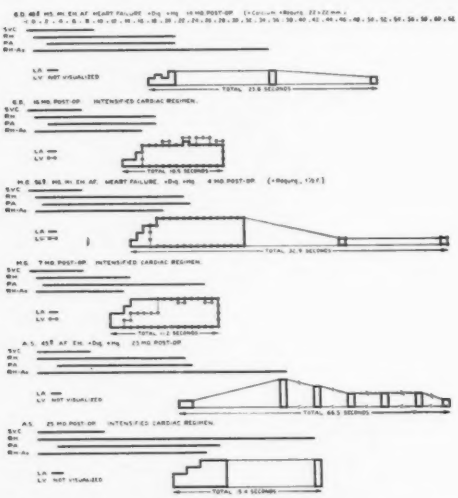

FIG. 5. Effect of intensified therapy for heart failure in individuals who had surgery. Angiocardiographic results in three individuals before and after intensification of medical therapy. The results of the second study for each individual are immediately below those of the first.

for mitral stenosis and that impaired left atrial emptying, as determined by this technique, can occur in those with mitral valve disease, regardless of whether stenosis, regurgitation or a combination of the two exists. Furthermore, similar findings may occur even in the absence of organic valvular disease. Lastly, there are no characteristic angiocardiographic features that can differentiate those who have had a mitral valvotomy from those who have not. This statement does not exclude the possibility that mitral valvotomy may produce changes in circulation times.

However, changes in circulation time with spontaneous change in myocardial function may occur or be due to medical treatment. The significance of medical treatment in changing the times of intracardiac flow through the heart can be shown in some individuals who have already had their mitral stenosis reduced by surgery. Figure 5 shows the effects of an intensified medical regimen in three individuals who had surgery 4 to 23 months before. All were said to have predominant mitral stenosis. Two had slight regurgitant jets after surgery. Note the long circulation times. The left atrial time is markedly prolonged. The second patient, M. G., was the only one who showed opacification of the left ventricle before intensification of medical therapy. After intensification of the medical regimen, the angiocardiogram was repeated. The results of the second study in each patient are shown immediately below those of the first study. The intracardiac

circulation time and the left atrial time are shorter and the degree of left atrial opacification is increased. In one, G. D., the left ventricle, previously not visualized, became greatly opacified.

This change following medical treatment indicates that the pattern of mitral stenosis in the same individual is more often seen in failure than in compensation, evidence of the importance of myocardial function. Changes of this sort are most quickly effected by digitalis and mercurial diuretics but can follow bed rest alone. Such changes can, at times, be demonstrated even in the absence of clinically evident heart failure and with an apparently adequately controlled ventricular response to digitalis in individuals with atrial fibrillation.

It is clear, therefore, that the angiocardiographic pattern of mitral stenosis differs in a characteristic manner from the normal but is not specific. It may occur in those with stenosis, regurgitation or both and even in the presence of nonvalvular heart disease. Moreover, our angiocardiographic technique is sensitive enough to detect changes that occur naturally or after medical treatment. Furthermore, we have found that the angiocardiographic pattern for mitral stenosis retains its characteristic features after mitral valvotomy. Since changes in circulation times or even in degree of opacification of chambers can occur with spontaneous changes in myocardial function or after medical therapy, a stable state of disability is prerequisite to determination of the specific effects of surgery. It is well known that two hearts considerably different in size may have identical outputs. Circulation times are related to cardiac output and residual volume among other factors. It appears to us, therefore, that a decrease in circulation times or a decrease in pulmonary pressure or both after mitral valvotomy in an individual with a preoperative stable state of disability would provide objective evidence of benefit specifically produced by surgery. On the other hand, no change or even a drop in pulmonary artery pressure associated with increase in circulation times would make it unlikely that surgery has improved cardiac function. A correlative study of pulmonary artery pressure and angiocardiographic circulation times is now in progress.

Summary and Conclusion

1. A study was made of individuals with and without cardiovascular disease using the biplane stereoscopic angiocardiographic apparatus (Chamberlain) with simultaneous recording of the carotid pulse.

2. Results are based primarily upon the findings in four individuals without cardiovascular disease, 22 with mitral stenosis and 31 with mitral stenosis and mitral valvotomy.

3. The duration and degree of opacification of each vessel or chamber was determined and the "volume" of the left atrium measured.

4. The intracardiac circulation time in persons with normal hearts did not exceed 6.3 seconds. In individuals with heart disease, it may be prolonged but does not exceed 9.1 seconds in the absence of atrial fibrillation, obvious puddling of contrast substance in the right ventricle, marked cardiomegaly or heart failure.

5. Normally, the right heart time, pulmonary artery time and left atrial time are approximately equal.

6. In mitral stenosis, there is a disproportionate prolongation of the pulmonary artery time and left atrial time. The left atrial time exceeds the pulmonary artery time and the latter, in the absence of right heart failure, exceeds the right heart time. The pulmonary artery and branches are variably enlarged.

7. In mitral stenosis, the left atrial "volume" was estimated to be twice to 12 times the normal. The left atrial "volume" usually but not always increases and not necessarily proportionately with increase in heart size. The increase in volume is not related to age or duration of the rheumatic state.

8. No relationship could be determined between left atrial time and left atrial size, or between left atrial and left ventricular opacification to distinguish "pure" mitral stenosis from mitral stenosis with regurgitation as diagnosed surgically, or to permit prediction of the degree of mitral stenosis as reported by the surgeon.

9. The angiocardiographic pattern of mitral stenosis is not diagnostic. It may occur in those

with stenosis, regurgitation or both or even in the presence of nonvalvular heart disease.

10. There are no characteristic angiocardiographic features that can differentiate those who have had a mitral valvotomy from those who have not.

11. Changes in circulation times occur with spontaneous changes in myocardial function and after medical therapy.

Summario in Interlingua

Le fluxo intracardiac de injectiones intravenose de materiales radio-opac esseva studiate per medio de rapide simultanee angiocardiographia stereoscopic biplan. Le tempores de circulation intracardiac assi determinate pote esser utile in le detection de anormalitates structural e de alterationes functional del corde. In stenosis mitral un distincte sed non specific configuration esseva constatabile, si o non valvotomia mitral habeva essite executate. Inter le dimensiones del atrio sinistre e le tempore del circulation sinistroatrial o inter le grado de opacitate del atrio sinistre e illo del ventriculo sinistre, il non esseva possibile establir relationes que haberea servite a differentiar "pur" stenosis mitral ab stenosis mitral con regurgitation (como isto esseva diagnosticate al tempore del intervention chirurgic) o a predicer le grado de stenosis mitral (que le chirurgo constatarea).

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Pyretotherapy and Subcutaneous Hexamethonium in the Treatment of Severe and Malignant Hypertension

By Pablo Thomsen, M.D., Ramón Ortúzar, M.D., Fernando Goñi, M.D., Cristobal Espíldora-Luque, M.D., and León Vial, M.D.

The permanent lowering of arterial pressure in cases of malignant and severe hypertension is of paramount importance. A new treatment that combines subcutaneous administration of hexamethonium with fever therapy produced by intravenous injections of bacterial vaccine is described. Reduction of blood pressure to normal levels and improvement of eye grounds, electrocardiogram, heart condition and subjective symptoms were obtained. The basis for these effects could be the potentiation of the action of hexamethonium produced by the induced fever.

THE seriousness of the picture of severe and malignant hypertension, the usually progressive nature of the resulting vascular alterations, and the meager results obtained in the majority of cases by the medical or surgical treatments that have been recommended warrant any therapeutic innovation which brings about a change for the better in this condition and promises a recession of the malignant features responsible for the sinister prognosis of such cases.

Pyretotherapy has been used for the past 30 years in the treatment of hypertensive retinopathy. The results obtained had been slightly different, but in general the reported cases have shown some improvement.[1, 2]

In 1944, Taylor and Page,[3] working on the hypothesis that certain renal extracts might contain hypotensive substances, injected such extracts and observed resulting pyretic crises together with marked hypotension and improvement of kidney function. The same authors reported their results with this method in experimental hypertension and later in hypertensive subjects, concluding that the results were encouraging in cases with preserved renal function, but varied with the pyretogenic substances employed.[4, 5] Other investigators,[6-9] have obtained comparable results, but they have dismissed this form of treatment because of the difficulties and suffering experienced by the patients.

We have not found any description of the use of hexamethonium combined with pyretotherapy, and have proposed it in the hope that the combination of the two methods would enhance the effects produced by each method singly and permit reduction of dosage or frequency of administration, thus avoiding undesirable side effects of hexamethonium and some of the discomfort of pyretotherapy.

This article reports the results obtained with combination of pyretotherapy and hexamethonium in 12 cases of severe and malignant hypertension.

Method

The patients treated were regarded as cases of severe and malignant hypertension by reason of the presence of the following features: (1) Diastolic hypertension above 115 mm. Hg, not modified by 10 days bed rest, salt-free diet and administration of usual dosage of phenobarbital, (2) progressive impairment of general condition, necessitating definite and enforced limitation of activity and (3) vascular damage as evidenced by changes in the eye grounds (five cases showed the complete picture of hypertensive neuroretinopathy), increase in size of the heart, and electrocardiographic signs of left ventricular strain with or without signs of myocardial alteration or coronary insufficiency.

Renal function, as determined by nitrogen retention, specific gravity of urine, concentration test and urea clearance, was variable, but those patients showing marked renal insufficiency were excluded

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The hexamethonium chloride used in this study was supplied through the courtesy of E. R. Squibb & Sons (as Bistrium) and Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y. (as Hexameton).

because of the risk of the proposed treatment in such cases.

The pyretogenic substance was Neurovaccine Beta, a water-soluble bacterial suspension containing in 1 cc. 50 million *Bacillus pyocyaneus*, 52.5 million *Staphylococcus aureus* and 25 million *Bacillus prodigiosus*. As hypotensive agents, injectable hexamethonium bromide and chloride were used. After termination of treatment, and with the hope of maintaining the favorable effects produced, therapy was continued with Apresoline and oral hexamethonium.

All patients were hospitalized. For the first 10 days, they were subjected to strict bed rest, salt-free diet, and the usual dosage of phenobarbital. Those patients who at the end of this time had a diastolic pressure below 115 mm. Hg were excluded.

Measurements of arterial pressure were for the most part taken by two persons only, 6 to 15 readings daily being made on each patient, the figure computed being the average of two determinations.

Treatment was begun by observing the response to injection of 10 to 20 mg. hexamethonium, and continued by administering 20 to 50 mg. one to four times in 24 hours. The size and frequency of the dose was determined by the influence on the blood pressure and the side effects produced. In some patients, total doses of 200 mg. of the ion were administered daily. At first the intravenous route was used, but, notwithstanding the recommendations of Freis, very marked declines of pressure occurred, for which reason the subcutaneous route was consistently used thereafter. Upon stabilization of the results thus obtained, pyretic injection was added for six days out of the week in doses increasing from 0.1 to 1 cc. to induce fever of over 102 F. In some patients, the febrile crises were spaced, insofar as maintenance of reduced blood pressure permitted, so that they occurred only two to three times per week. Aminopyrin was used to alleviate the distress attendant upon the thermal reaction, and when declines in arterial pressure were too marked, the foot of the bed was elevated, generally with satisfactory response. We did not resort to pressor amines in such cases because in patients with malignant hypertension, cardiac accidents may result. Moderate restriction of salt was maintained during the treatment.

Results

Tables 1, 2 and 3 show the clinical features presented by our cases and the changes produced in the blood pressure, eye grounds, electrocardiogram, cardiac condition, subjective symptoms and general condition, and renal function.

Arterial Pressure. Aside from the drops in pressure directly related to administration of hexamethonium, there was an observable gradual decline in pressure measured under basal conditions, immediately after the patient awoke from sleep. After the first weeks of treatment, there were not even isolated recurrences of the high control figures, and the pressure curve tended to stabilize at figures around 170/90 (figs. 1 and 2).

Table 1.—*Numerical Data*

Case No.	Sex	Age	Known Duration of Hypertension Years	Duration of Treatment Days	No. of Pyrogenic Injections	Hospitalization Days
1	F	50	5	48	18	67
2	F	44	9	82	48	303
3	M	57	5	33	12	84
4	M	50	11	58	46	203
5	M	53	4	54	42	106
6	M	54	3	36	30	137
7	M	48	2	54	26	134
8	F	49	10	15	7	36
9	F	48	12	23	8	90
10	F	45	4	2	2	129
11	F	36	6	87	36	273
12	F	41	4	40	20	80

The correlations found between administration of hexamethonium and pyretic injections are illustrated in figures 3 and 4.

Eye Grounds. The changes in the ocular fundi of the patients (cases 2, 4, 5, 11 and 12) with hypertensive neuroretinopathy (group IV), were favorably modified to an appreciable extent in all instances. There was no substantial change in the cases manifesting only sclerosis, nor in two patients in whom treatment was suspended prematurely. A striking feature was the marked diminution of hemorrhage when present. Vision improved consistently in those cases where it had been impaired.

Electrocardiogram. Of the 11 patients who received treatment of satisfactory duration, one had a normal electrocardiogram at the beginning of treatment. Of the other 10 patients, the abnormal electrocardiogram became normal in four (figs. 5, 6 and 7) except for persistence of left axis deviation; in three cases the height of the T wave in lead I increased more than 1 mm., and in three cases no change occurred.

Cardiac Condition. At the start of our studies

TABLE 2.—*Clinical Data before Treatment*

Case No.	General Condition	Cerebral Involvement	Renal Involvement	Cardiac Involvement	ECG	Eye Grounds	Pressure
1	bad	Hemiparesis	0	Dysp.; card. asthma; L.V. hyper.	L.V. strain	Marked sclerosis.	250/145
2	bad	0	Urea Cl. 24%; albumin.; cylindruria.	Dysp.; card. asthma; L.V. hyper.	L.V. strain	Papilledema; hemor.; exudates; gen. constrict.	230/130
3	poor	Pseudobulbar syndrome	0	Mild angina; L.V. hyper.	L.V. strain	Marked gen. and focal constrict.; mod. sclerosis.	205/120
4	poor	0	Albumin; cylindruria.	Gallop; mod. angina; L.V. hyper.	Marked myocard. damage	Sl. papilledema; hemor.; exudates; mod. sclerosis.	230/125
5	bad	Hypertens. encephalop.; diplopia	Urea Cl. 30%	L.V. hyper.	L.V. strain	Papilledema; hemor.; exudates; marked constrict.	230/150
6	poor	0	0	L.V. hyper.	L.V. strain	Marked constrict.; mod. sclerosis.	200/125
7	poor	0	Albumin.; cylindruria.	0	Normal	Sl. blur. of the disk; mod. sclerosis.	195/125
8	poor	0	0	L.V. hyper.	L.V. strain	Hemor.; exudates; mod. sclerosis.	220/120
9	bad	Hemiparesis	Urea Cl. 37%; albumin.; cylindruria.	L.V. hyper.	L.V. strain	Hemor.; marked sclerosis.	230/130
10	poor	0	0	0	Normal	Mod. sclerosis.	205/115
11	bad	0	0	L.V. hyper.	L.V. strain	Marked papilledema; exudates; marked sclerosis.	200/115
12	poor	0	0	L.V. hyper.	L.V. strain	Papilledema; mod. sclerosis.	230/125

TABLE 3.—*Results of Treatment*

Case No.	Pressure	Renal Involv.	Eye Grounds	Vision	ECG	Heart Involv.	General Condition	Headache Dizziness
1	177/104	0	0	++	+	+	+	++
2	170/90	0	+++	+++	+++	+	+++	+++
3	170/105	0	+	0	+++	+	−	0
4	170/90	+	++	0	++	++	++	+++
5	175/100	0	+++	+++	+++	0	+++	+++
6	145/85	0	0	0	+	0	+	+++
7	140/90	+	0	0	0	0	+	+++
8	155/85	0		0	+	0	−	+
9	170/95	0	++	0	0	0	−	0
10	70/40	0	0	0	0	0	−	0
11	151/94	0	+++	+++	+++	0	+	+++
12	170/100	0	++	0	0	0	+	+++

The results of the treatment have been evaluated according to the following convention: +++ marked improvement; ++ moderate improvement; + slight improvement; 0 no change; − worse.

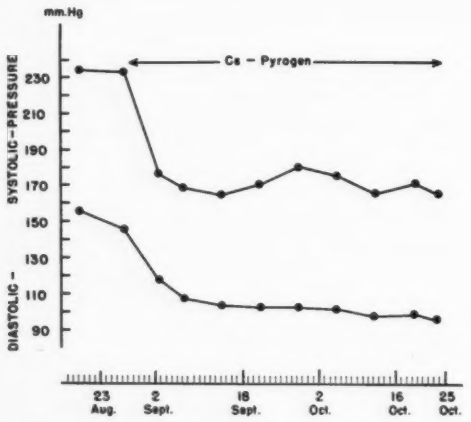

FIG. 1. Case 5. Malignant hypertension. Papilledema, cotton-wool patches, hemorrhages. Vision greatly impaired. Urea clearance 30 per cent. Hypertensive encephalopathy, paresis of rectus externus, diplopia. Electrocardiogram shown in fig. 6. Slight reduction of arterial pressure after two weeks of Kempner diet, sedatives and bed rest. Each point represents at least 35 determinations of pressure, all being recorded with the patient in the supine position.

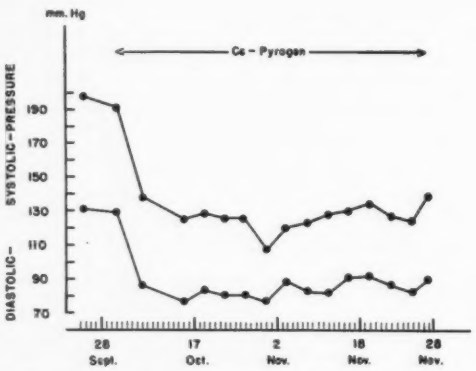

FIG. 2. Case 8. White man, 48 years old, with progressive hypertension of two years' duration. Incapacity for work forced him to give up his employment. No improvement with bed rest, salt free diet, sedatives. Good response to treatment.

definite cardiac insufficiency was present in three patients. There was complete recovery in two, and substantial improvement in one. In one additional patient an anginal syndrome disappeared. There was no appreciable reduction of cardiac size in any instance.

Subjective Symptoms and General Condition. The symptoms due to hypertension disappeared in all but one patient. The general condition improved in seven cases, was unchanged in two, and deteriorated in three owing to intolerance to treatment and vomiting in one case, intercurrent gastrointestinal hemorrhage in another, and arthralgia and general prostration in the third. There was considerable loss of weight in one patient.

Kidney Function. Renal function did not change substantially, but in three patients there were frequent and transitory elevations of blood urea, related to persistent vomiting which necessitated temporary suspension of treatment. In two cases, a pre-existing albuminuria disappeared.

Complications. Acute hypotension, with prolonged syncope necessitating suspension of treatment, was observed in one case. Marked lowering of pressure, which responded to elevation of the feet, was observed on numerous occasions in many patients. Anginal pain appeared in some of these patients during the hypotensive phase, in one instance with electrocardiographic manifestations.

Transitory nitrogen retention, with oliguria as stated previously, was observed in three cases where there was vomiting due to intolerance of the treatment.

Marked arthralgia, myalgia and prostration accompanied the induced fever in the majority of cases, and accounts for resistance of patients to prolonged treatment. Aminopyrin definitely lessened the severity of the symptoms. Constipation, meteorism, vesical paresis and changes in accommodation, all signs related to the effect of hexamethonium on the autonomic nervous system, were observed in nearly all patients in varying degrees.

DISCUSSION

There is now sufficient evidence to support the hypothesis that the high level of diastolic pressure maintained in small arteries and arterioles is the chief, if not the only, cause of malignant hypertension.[10–12]

The view that the extent of hypertension is the major known factor determining malignancy brings us to the conclusion (1) that

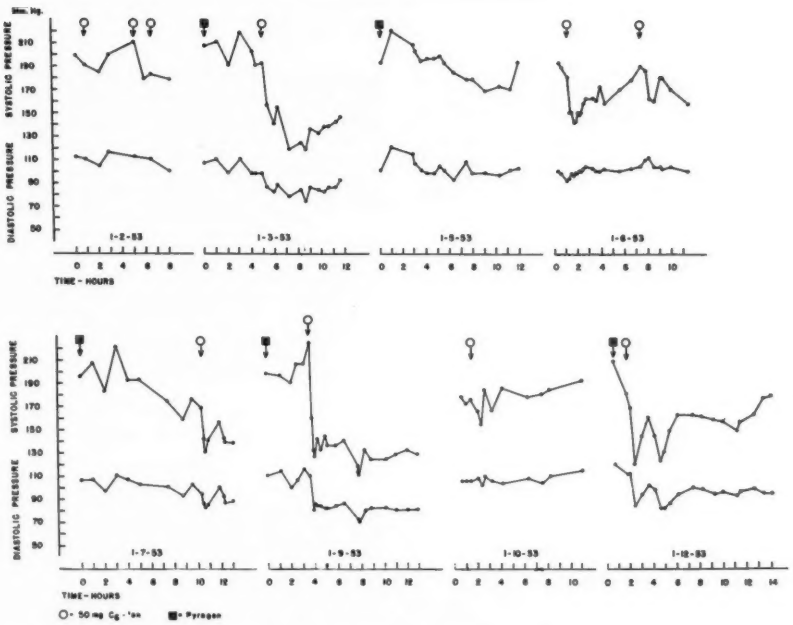

FIG. 3. Case 4. All pressures recorded in supine position. 1–2–53 slight hypotensive response to 50 mg. hexamethonium ion; during the previous weeks the patient had received progressive doses of hexamethonium that were effective at that time. 1–3–53 pyrogen and five hours later 50 mg. hexamethonium ion with marked hypotensive effect. 1–5–53 effect on blood pressure of pyrogen alone. 1–6–53 mild action of hexamethonium. 1–7–53 pyrogen and 50 mg. hexamethonium ion 10 hours later with a slight response, but the summation of the hypotensive effects of fever and of hexamethonium resulted in a low level of pressure. 1–9–53 pyrogen and 50 mg. hexamethonium ion three hours later, a marked and sustained reduction of blood pressure is obtained. This represents potentiation of hexamethonium by pyrogen. 1–10–53 slight effect of hexamethonium. 1–12–53 50 mg. of hexamethonium ion one hour after pyrogen; also a potentiation of hexamethonium.

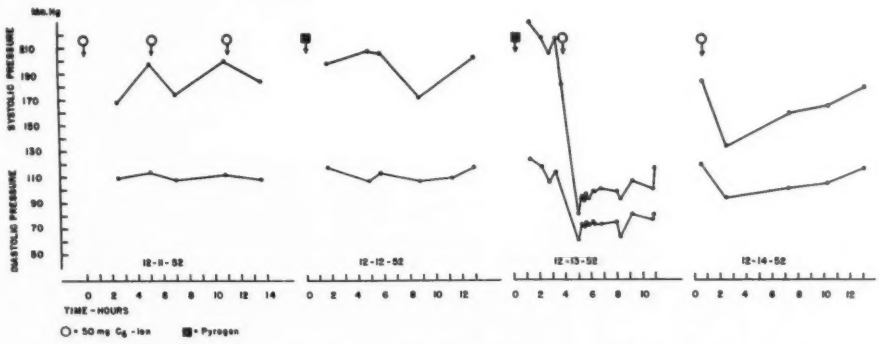

FIG. 4. Case 8. All pressures recorded in supine position. 12–11–52, development of tolerance and poor response to hexamethonium. 12–12–52, no pressure change with pyrogen. 12–13–52, pyrogen plus hexamethonium three hours later. Prolonged and accentuated hypotension. 12–14–52, increased response to hexamethonium.

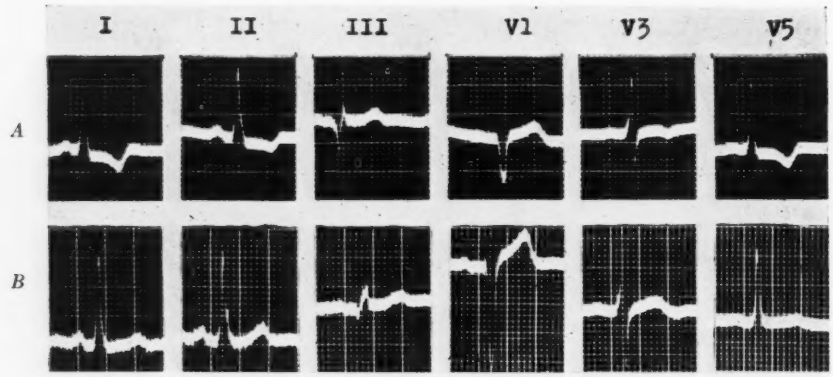

FIG. 5. Case 3. *A*, 1-9-52, before treatment. Marked hypertensive pattern with slight left axis deviation. *B*, 8-29-52 after five weeks of treatment. Marked improvement.

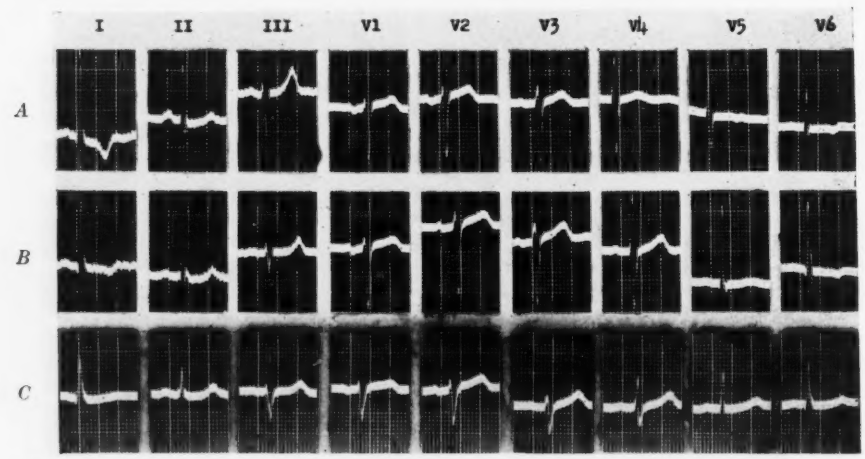

FIG. 6. Case 5. *A*, 8-19-52, before treatment. Left ventricular strain. *B*, 9-17-52, after two weeks of treatment. T wave less inverted in lead I, higher in leads V_3 and V_4, and positive in lead V_5. *C*, 10-28-52, after eight weeks treatment. Further improvement, disappearance of S-T depressions, T wave isoelectric in lead I, T wave positive in precordial leads.

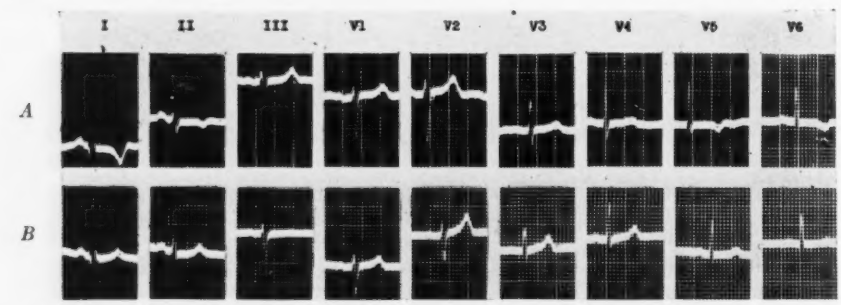

FIG. 7. Case 11. *A*, 10-24-52, before treatment. Well marked left ventricular strain pattern. *B*, 12-7-52, after five weeks of treatment. Marked improvement; T wave positive in standard and precordial leads.

malignant hypertension may appear in any type of *severe hypertension* which is accompanied by sustained high diastolic pressures, and (2) that if the arterial pressure is reduced sufficiently before there is major renal impairment, recession of the syndrome to a benign form of hypertension may be possible. This would be what we might call a "reversible phase of malignant hypertension."

The correctness of the former statement has been demonstrated by the description of cases with the clinical and histological features of malignant hypertension in which the elevation of blood pressure was due to chronic pyelonephritis, periarteritis nodosa, pheochromocytoma, Cushing's syndrome, chronic lead poisoning and chronic nephritis.[13–17] Pickering has pointed out that the only form of hypertension known in which hypertensive neuroretinopathy, progressive renal insufficiency and arteriolonecrosis have not been observed is aortic coarctation.[18]

That sustained reduction of arterial pressure will eliminate malignant features appears from the observations of Smithwick,[19] Hammertrom and Beechgaard[20, 21] and Pickering.[18]

From these observations it may be inferred that when the malignant phase appears in any type of arterial hypertension, it is imperative to seek to reduce the blood pressure in order to prolong the life of the patient. When the original hypertension is so-called "essential hypertension," hope may be entertained of securing regression to the benign form, with its far more favorable prognosis, especially if pressure within acceptable limits can be maintained. The treatment we have used in our patients apparently produced these results, having not only systematically reduced the pressure but also favorably altered the aspect of the eye ground in those patients who had hypertensive neuroretinopathy.

Kidney function, on the other hand, in those patients in whom it had seriously deteriorated, underwent no change. Indeed these patients sometimes showed an increase in nitrogen retention, such increase being associated in the majority of cases with gastrointestinal disturbances, diarrhea or vomiting, accompanied by oliguria. On other less frequent occasions, rise in uremia was linked with excessive and sustained declines of pressure.

In those patients in whom pyretotherapy was discontinued but hexamethonium alone or in combination with Apresoline continued, the pressure has remained at satisfactory levels and the subsequent course so far has been that which is characteristic of benign essential hypertension. In the patients in whom therapy with oral hexamethonium and Apresoline was not continued for lack of drugs, a return to the initial arterial pressure values was observed.

Taylor and Page,[4] in their series of 20 patients treated by pyretotherapy alone, found marked improvement of electrocardiogram in 11 patients and moderate improvements in the remaining 9. White and his co-workers,[22] discussing the results obtained in operations by Smithwick, noted an increase of more than 1 mm. in the height of the T wave in lead I in 47 per cent of the patients. Doyle,[23] found improvement of the electrocardiograms of 76 per cent of the patients treated by Smirk with hexamethonium. The improvement appeared to be proportional to the degree of control of arterial pressure gained by the treatment. Our series is smaller, but generally accords with the results of Doyle.[23]

The first parenteral administration of hexamethonium produced sudden and prolonged drops of pressure. Subsequent doses, even if larger, had less effect, and the daily pressure curve was highly irregular during this period. In some cases, the maximum doses administered were ultimately without effect. Upon institution of pyretotherapy, hexamethonium regained its effectiveness, and the blood pressure levels present after the effect of the drug had worn off, were below those preceding pyretic injection. Thus a gradually descending curve was established, permitting wider spacing of febrile crises while sustaining their immediate favorable effects.

It was also possible to show that the sensitization to hexamethonium resulting from pyretic injection begins minutes after injection and remains marked for as long as seven hours, and, at times, continues into the following day. Induction of fever is not necessary to secure lowering of pressure and potentialization of the

effects of hexamethonium, satisfactory results being obtained when fever is suppressed with antipyretics. Add to this the fact that the potentiating effect of the pyretic injection on the action of hexamethonium manifests itself almost immediately upon injection, prior to appearance of fever, and we may assume that it is not the temperature rise in itself that produces the results obtained, but that these results are due to other mechanisms having to do with the injection of foreign protein. The term "pyretotherapy" would then be inappropriate, and we might more correctly speak of intravenous bacterial proteinotherapy.

It may well be asked whether the results obtained in our cases were effected exclusively through the drop in pressure produced by the combined therapy, or whether fever also acted through some other mechanism. Selye[24] feels that pyrogenics are definitely powerful "stressors" which might, at least in part, act to correct a generalized modified alarm syndrome.

Again, the increase in renal circulation produced by the fever might be a beneficial factor in the correction of hypertension.

Summary and Conclusions

(1) So-called "pyretotherapy" by bacterial vaccines, used alone, is capable of producing major declines of pressure in patients with severe and malignant hypertension, but very frequent injections are required and poorly tolerated by the majority of patients.

(2) Injectable hexamethonium induces hypotension in many patients with severe and malignant hypertension, but habituation to the drug sets in rapidly and necessitates increase of dosage to values producing intolerable effects.

(3) Combination of hexamethonium and pyretotherapy has been shown to be capable of markedly reducing pressure levels in patients with severe and malignant hypertension, at the same time improving eye ground and vision, electrocardiogram, cardiac condition and subjective symptomatology.

(4) This combination has made it possible (a) to space the pyretic injections so as to render prolonged treatment more tolerable, and (b) to reduce the daily dose of hexamethonium to values that do not cause major side-effects.

(5) The source of this advantage would appear to lie in an increased sensitivity to hexamethonium produced by the pyretic injection.

(6) These results are not linked with the temperature rise, since they occur before the latter has appeared, persist after it has disappeared, and are present when fever is prevented with antipyretics.

(7) This treatment appears to be advisable in patients with severe and malignant hypertension resistant to hexamethonium or other therapeutic means now employed. In our experience it has also been useful in cases resistant to combination of hexamethonium and Apresoline.

(8) The treatment requires hospitalization of patients and continuous medical supervision.

Acknowledgment

The authors acknowledge with pleasure the technical help given by Miss Elena Anticevic and Miss Elena González.

Summario in Interlingua

In casos de sever e maligne hypertension le reduction permanente del pression arterial es de importantia cardinal. Es describite un nove tractamento que combina le administration subcutanee de hexamethonium con un therapia a febre producite per le injection intravenose de vaccino bacterial. Esseva obtenite le reduction del pression sanguinee a nivellos normal e le melioration del fundo del oculos, del electrocardiogramma, del condition del corde, e del symptomas subjective. Il es possibile que le base de iste effectos es a cercar in un potentiation del action de hexamethonium per le febre resultante del injection bacterial.

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A Study of the Spatial Vectorcardiogram in Subjects with Anterior Myocardial Infarction

By G. E. Burch, M.D., Leo Horan, M.D., and J. A. Cronvich, M.S.

In 20 subjects with anterior myocardial infarction the early portions of the QRS sÊ-loop were directed away from the area of infarction. Deformities that occurred in later portions of the QRS sÊ-loop were compatible with loss of electric force produced by depolarization of areas activated late in the phase of depolarization. This observation is of significance because electrocardiograms, as conventionally recorded and interpreted, fail to detect infarcts located in areas of the heart that are depolarized late and that would not be expected to deform the early portions of the QRS complex sÊ-loop.

THE influence of anterior myocardial infarction upon the spatial vectorcardiogram has interested several investigators,[1-5] but none of their studies here included extensive use of the equilateral tetrahedral system of electrode placement, and some have not used it at all. The present investigation of anterior myocardial infarction was concerned not only with a description of the spatial vectorcardiogram obtained with the equilateral tetrahedral reference frame but also with the possible influence of infarction in areas of the heart that are depolarized late upon those portions of the QRS sÊ-loop that are inscribed late. This is of particular interest because the QRS complex, as conventionally recorded electrocardiographically, may reveal infarction in those portions of the myocardium that are depolarized early during excitation. As discussed previously in a spatial vectorcardiographic study of posterior myocardial infarction,[6] it is theoretically possible for an infarct to be so localized in an area of the heart that diagnostic alterations in the conventional electrocardiogram are indefinite or unrecognizable.

Methods and Materials

The method for recording the spatial vectorcardiogram (sVCG) is that previously described with the use of the equilateral tetrahedral reference frame.[7-8] Electrocardiograms were recorded, as previously described,[9] a few minutes before or after recording of the sVCG with the subject lying in bed in the same position for both studies. Electrocardiograms recorded at other times for routine clinical purposes were also studied and integrated into the investigations of these subjects.

Twenty subjects with anterior myocardial infarction were observed, 18 were ambulatory outpatients of the Charity Hospital. Because a mobile vectorcardiograph was not previously available, only two of the subjects included in this series had recent infarcts at the time the recordings were obtained; the remainder were ambulatory and their infarcted areas were clinically healed. Table 1 summarizes the clinical data on the subjects. Postmortem confirmation was available for only two subjects; the basis for the diagnosis of anterior myocardial infarction in the other 18 subjects consisted of a typical clinical syndrome supported by serial laboratory and electrocardiographic data. Whenever the diagnosis was doubtful, the subject was not included in this series. The clinical diagnosis of ventricular hypertrophy was made only in the presence of a likely etiologic factor and of either fluoroscopic or postmortem evidence of ventricular enlargement.

Four subjects had complete bundle branch block (right or left) and 12 had left ventricular hypertrophy (table 1).

Results

All QRS sÊ-loops in this series (figs. 1 to 7) were readily recognized as being different from the normal types 1 and 2 described for normal young adults.[9]

The QRS sÊ-loop. The mean instantaneous vectors of the early portions of the QRS sÊ-loop were directed away from the areas of

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TABLE 1.—*Clinical and Vectorcardiographic Data in Twenty Subjects with Anterior Myocardial Infarction*

Subject No.	Age (Yrs.)	Clinical Diagnosis*	Interval Between Infarction & sVCG†	Evidence of LVH	Maximal Mean QRS				Instantaneous Axes T				Displacement J				Posterior Extent of the Maximal QRS Vector mv	Rotation of sÊ-loop	
					Frontal		Sagittal		Frontal		Sagittal		Frontal		Sagittal			Frontal‡	Sagittal‡
					mv	angle	mv	angle	mv	angle	mv	angle	mv	angle	mv	angle			
1	40	ASHD with CHF	3 wks		0.51	−51°	0.47	−57°	0.08	105°							0.25	CC	CC
2	67	ASHD	17 mths		0.59	−4°	0.22	46°									0.20	CC	CC
3	79	ASHD	5 mths	+	0.41	−22°	0.27	−38°	0.05	82°	0.05	99°	0.05	−132°	0.04	−103°	0.22	8	8
4	64	SHD with CHF, AP	5 mths	+	1.47	−64°	1.70	−48°	0.21	139°	0.22	130°	0.16	133°	0.19	143°	1.27	CC	8
5	49	HCVD with AP	5 wks		1.26	−8°	0.56	−47°									0.37	CC	CC
6	48	HCVD	3 wks	+	1.06	−14°	0.64	−25°	0.03	95°	0.08	102°	0.06	142°	0.07	161°	0.56	CC	CC
7	59	ASHD	2 wks		1.21	40°	0.83	116°	0.28	−154°	0.10	−99°					0.69	CC	CC
8	59	ASHD with CHF	35 mths		0.48	−76°	0.80	−28°									0.70	CC	8
9	54	ASHD	2 wks		1.00	−58°	0.87	−81°	0.19	−130°	0.19	−139°					0.25	C	C
10	50	HCVD	3 wks	+	0.87	117°	0.78	94°	0.20	21°	0.10	89°	0.15	−8°			0.	C	C
11	62	ASHD with CHF, AP	11 mths	+	0.57	−56°	0.65	−40°	0.22	118°	0.24	138°	0.06	43°	0.14	175°	0.50	8	CC
12	63	ASHD and Raynaud's dis.	7 mths	+	0.67	75°	0.75	129°	0.24	99°	0.29	130°	0.10	−103°	0.09	−79°	0.43	CC	CC
13	70	ASHD	3 wks		0.52	−69°	0.50	−113°	0.35	−117°	0.25	−84°					1.00	8	8
14	64	ASHD with CHF, AP	39 mths	+	1.20	−87°	1.56	−48°	0.19	105°	0.28	144°					1.00	C	C
15	84	ASHD with AP	10 yrs		1.30	−65°	1.09	−57°	0.09	−88°	0.13	−53°	0.13	140°			0.61	CC	CC
16	55	ASHD	11 mths		0.48	−77°	0.67	−36°									0.52	CC	CC
17	53	ASHD	4 wks		0.68	84°	0.65	80°	0.25	−156°	0.20	−31°					0.43	C	C
18	47	ASHD with CHF, AP	5 wks	+	0.60	3°	0.33	113°									0.	C	T
19	39	Direct injury to heart	25 yrs		0.48	−70°	1.00	−20°									0.93	CC	C
20	76	ASHD	3 wks	+	0.54	−72°	0.70	−46°	0.15	110°	0.18	135°					0.50	CC	T

* ASHD = Arteriosclerotic heart disease
SHD = Syphilitic heart disease
HCVD = Hypertensive cardiovascular disease
CHF = Congestive heart failure
AP = Angina pectoris
† wks = Weeks
mths = Months
yrs = Years
‡ C = Clockwise rotation
CC = Counterclockwise rotation
8 = Figure-of-eight configuration
T = "On-edge" or linelike

Note: Postmortem confirmation was obtained for subjects 9 and 12. All subjects were male except subjects 7 and 16. Right bundle branch block was also present in patients 2, 8 and 10; the QRS was prolonged (0.11–0.12 sec.) in subjects 4, 14 and 15.

infarction (fig. 1), a characteristic previously described.[10-12] For example, in figure 1 the infarct apparently was located in the anterior and septal region of the heart near the spiral and diaphragmatic locations, and the early vectors were directed towards the subject's left, superiorly, and posteriorly, that is, essentially away from the infarcted zone.

Many of the QRS sÊ-loops had sharply defined deformities in contour, some consisting of relatively smooth arcs (fig. 1), whereas others had segments that were straight, tending to produce sharp angulations in the loop (figs. 2, 3). When there were two or three straight segments in a loop, the QRS sÊ-loop tended to assume a triangular or rectangular configuration (figs. 2 and 3). These alterations in contour occurred in any portion of the loop, late and midportions as well as early portions.

The presence of left ventricular hypertrophy in subjects with anterior myocardial infarction tended to add to the existing configuration of the QRS sÊ-loop, described previously for left ventricular hypertrophy alone.[13] Accordingly, the resultant QRS sÊ-loop was large and oriented in the first and sixth sextants of the triaxial reference system in the frontal plane and posteriorly and in the first and sixth sextants of a triaxial reference system applied to the left sagittal plane (fig. 4). The QRS sÊ-loop usually had a smooth contour, which was distorted, in part at least, by alterations in the spatial vectors caused by death of muscle in the infarcted zone (fig. 1) and by disturbances in the order of depolarization such as exist with bundle branch block (fig. 3). Left ventricular hypertrophy also tended to increase the duration of the QRS sÊ-loop.

In subject 9 with infarction of the anterolateral region of the free wall of the left ven-

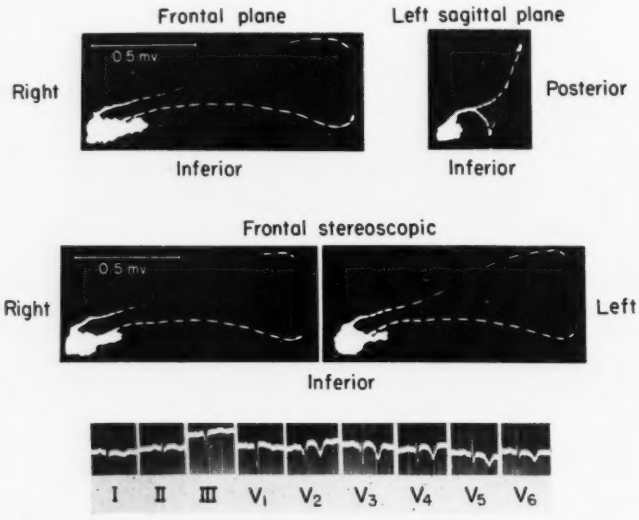

FIG. 1. Spatial vectorcardiogram and electrocardiogram of subject 5 with an anteroseptal myocardial infarct extending onto the diaphragmatic surface of the heart and with left ventricular hypertrophy. The early portion of the QRS sÊ-loop consists of vectors in the first sextant of the frontal and left sagittal planes, i. e., directed superiorly, posteriorly and to the left. The spatial vectorcardiogram shows the configuration and orientation characteristic of left ventricular hypertrophy.[13] The efferent limbs of the QRS sÊ-loop are arched superiorly, probably because of the loss of those electric vectors associated with depolarization as a result of infarction of the diaphragmatic surface of the heart near the apex. The loops in all illustrations, unless otherwise stated, are traced in the direction of the blunt end of the interrupted segments of the trace. The labels indicate the reference directions with respect to the subject.

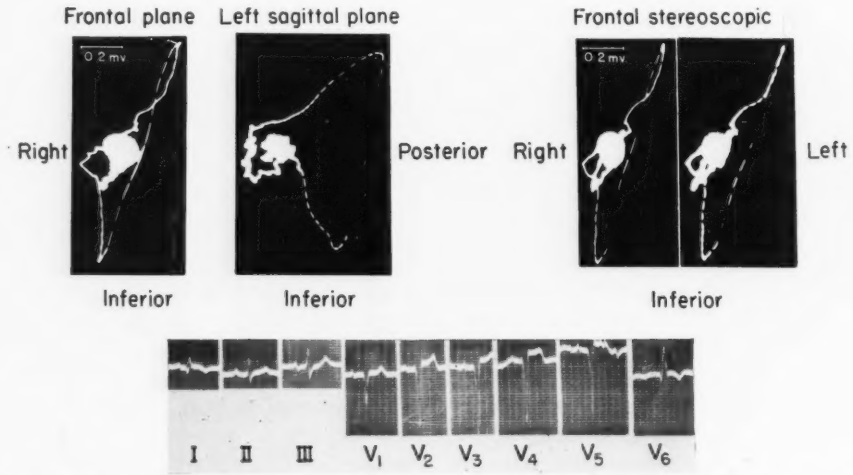

FIG. 2. Spatial vectorcardiogram and electrocardiogram of subject 11 with a large anterolateral myocardial infarct and left ventricular hypertrophy. Note the triangular shape of the QRS sÊ-loop in the left sagittal plane projection. The early portion of the QRS sÊ-loop is directed away from the area of infarction. The triangular shape of the QRS sÊ-loop may be due to loss of electric activity in those areas of infarction that are usually depolarized later in electric systole.

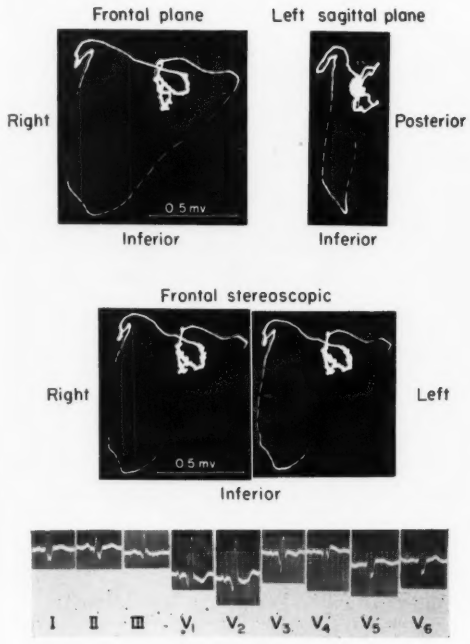

FIG. 3. Spatial vectorcardiogram and electrocardiogram of subject 10 with a large anterior myocardial infarct involving the anteroseptal, apical and diaphragmatic surfaces of the heart and with complete right bundle branch block. The early portions of the QRS sÊ-loop are directed away from the infarcted area and reveal the influence on depolarization of the infarcted zone, whereas the later and terminal portions are oriented to the right and anterior to the isopotential point (ip) and manifest the influences of right bundle branch block on depolarization. J is oriented superior to, anterior to, and to the left of ip, whereas the T sÊ-loop is located mainly inferior and posterior to ip.

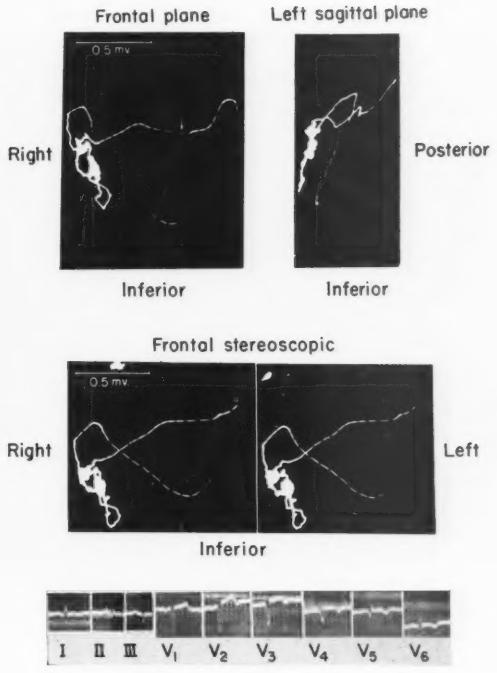

FIG. 4. Spatial vectorcardiogram and electrocardiogram of subject 3 with large apical myocardial infarction of the anterolateral, apical, and diaphragmatic surfaces of the heart and with left ventricular hypertrophy. The QRS sÊ-loop manifests the influences of these states in that the early portion of the loop is directed superiorly, posteriorly and then to the left; the midportion of the loop is spatially oriented superiorly, posteriorly and to the left.

tricle and the anterior half of the septum near the base, the early portion of the QRS sÊ-loop was displaced inferiorly, anteriorly, and to the right of the isopotential point (ip) (fig. 5). This subject also had left ventricular hypertrophy, which caused displacement of the later portions of the QRS sÊ-loop superiorly and posteriorly, and to the left of ip (fig. 5). All of these anatomic changes were confirmed at autopsy one month later, with the additional finding of recent pulmonary embolism.

The Junction J. In most instances the junction, J, could not be sharply localized because of interfering currents from skeletal muscle, noises in the amplifiers, and extraneous sources. In some instances, however, and especially when the shifts from ip were large, the point at which the QRS sÊ-loop ended and the T sÊ-loop began (corresponding to the junction, J) was readily identified. In the presence of left ventricular hypertrophy, J was displaced to the right, anteriorly, and slightly superior or inferior to ip (fig. 5). This varied somewhat, however, as shown in figures 2 and 6, when it was slightly superior to and to the left of ip. In subject 10 with right bundle branch block (fig. 3), J was oriented anterior to, to the left of, and only slightly superior to ip, whereas the T sÊ-loop began at J but rapidly rotated in-

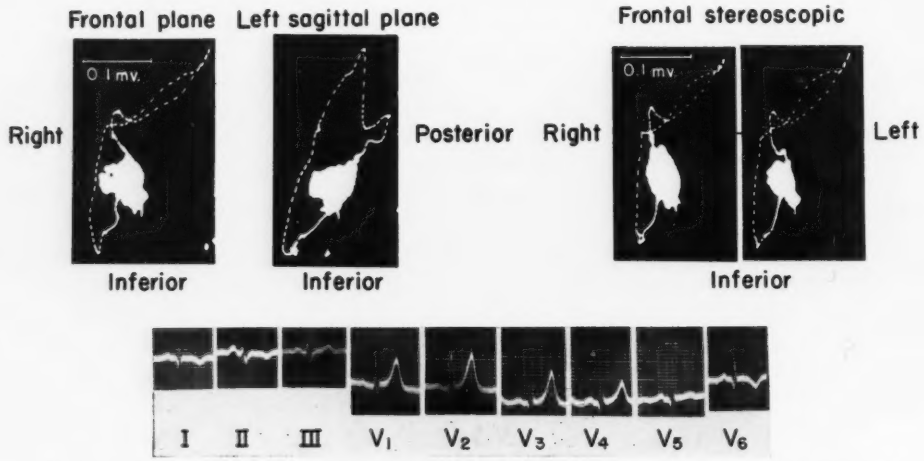

FIG. 5. Spatial vectorcardiogram and electrocardiogram of subject 9 with high lateral myocardial infarction of the left ventricle with left ventricular hypertrophy confirmed at autopsy. The early portion of the QRS sÊ-loop is directed inferiorly, anteriorly and to the right of the isopotential point (ip), and away from the area of infarction. The direction of inscription in this recording is toward the pointed end of the interrupted segments. The mid and terminal portions of the loop manifest evidences of left and right ventricular hypertrophy, respectively. Although right ventricular hypertrophy was not demonstrated at autopsy, the presence of a recent pulmonary embolism may make the latter observation significant. J is oriented superior and anterior to and to the left of ip whereas the T sÊ-loop is spatially oriented anteriorly, to the right, and essentially in the same horizontal plane with ip. J and the T sÊ-loop are poorly shown because of the halo but were discernible in the original photographic negatives.

feriorly and posteriorly and to the left of ip (fig. 3).

As were the configuration of the QRS sÊ-loop and spatial orientation of the T sÊ-loop, so too was the spatial orientation of J influenced by complicating cardiac disease states, such as ventricular hypertrophy, bundle branch block, pre-existing infarction, diffuse and local myocardial degeneration due to systemic disease, digitalis therapy, and extracardiac disease that influenced the electric field and cardiac position. In the subjects without any complicating cardiac disease except coronary disease (subject 13), the T sÊ-loop tended to be displaced away from the infarcted area (fig. 7), as would be expected from existing electrocardiographic knowledge.[10, 11] Furthermore, in these subjects, the T sÊ-loop was often narrow and, in general, had the configuration of a normal T sÊ-loop, differing primarily in spatial orientation (fig. 7).

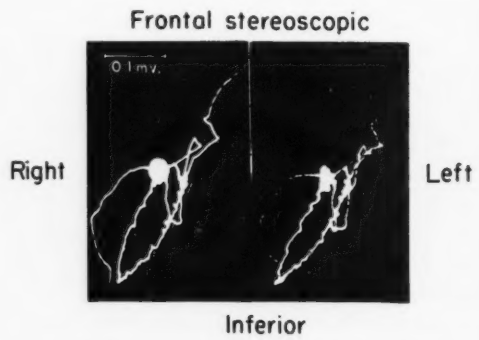

FIG. 6. The spatial vectorcardiogram shown in figure 2, recorded at greater gain to show J and the T sÊ-loop in anterolateral myocardial infarct in detail. J is oriented superiorly, anteriorly and to the left of the isopotential point (ip) or is displaced in the direction of the infarcted zone, whereas the T sÊ-loop is spatially oriented inferiorly, anteriorly and to the right of ip, as is to be expected in anterolateral infarction and left ventricular hypertrophy, according to existing principles in electrocardiography.

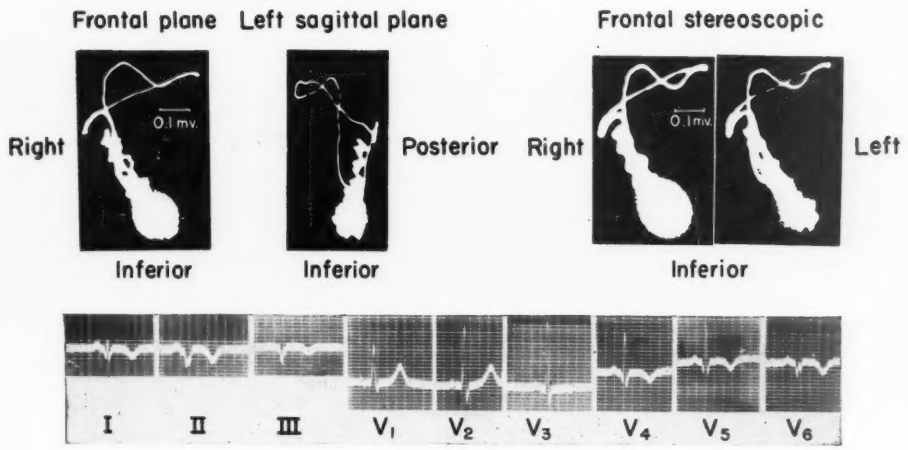

FIG. 7. Spatial vectorcardiogram and electrocardiogram of subject 13 with diaphragmatic and posterolateral myocardial infarction. The QRS sÊ-loop manifests the influences of these lesions. The T sÊ-loop (not shown well because of the halo) is narrow and spatially oriented superiorly, posteriorly, and to the right of the isopotential point (ip), or characteristically away from the infarcted area. The arch of the efferent limb of the QRS sÊ-loop that is superior to and to the right of ip, i. e., away from the infarcted area, is a characteristic discussed in the text as a possible deformity of the QRS sÊ-loop that may be a frequent and significant manifestation of infarction.

DISCUSSION

The spatial orientation of the early portions of the QRS sÊ-loop in subjects with anterior myocardial infarction conformed with existing knowledge in electrocardiography.[7, 10-12] The early mean instantaneous electric vectors caused by depolarization were directed away from the zone of infarct. Because of the complicating cardiac states and the limited number of records for study, it was not possible to identify in time and space the important mean instantaneous vectors that may be particularly influenced by the area of infarction. Therefore, it was decided, as previously,[6] to refer only to the early portions of the QRS sÊ-loop. Furthermore, in these subjects the anterior infarcts included infarcts in the septal region, anterior surface, apical area, and lateral surface. In several instances it was likely that the infarct extended onto the anterior part of the diaphragmatic surface of the heart. The area of infarction that influenced the order of depolarization most and earliest in the electric cycle would seem to have the most significant influence upon the orientation of the early portions of the QRS sÊ-loop. Apparently, the magnitude and temporal relationships of the component areas of depolarization were important in determining the spatial orientation of the mean instantaneous vectors.

The early portion of the QRS sÊ-loops of eight subjects in this series was directed to the left, superiorly, and posteriorly (fig. 1); these subjects had electrocardiographic evidence of anteroseptal infarction. In 10 subjects it was directed inferiorly and either slightly anteriorly or posteriorly and slightly to the right (fig. 3); these subjects had involvement of the lateral wall of the left ventricle. In two subjects with electrocardiographic evidence of only lateral wall involvement, the early portion of the QRS sÊ-loop was directed inferiorly, anteriorly, and to the right (fig. 5). When involvement of the diaphragmatic surface of the heart also existed, as it did in four subjects, the early portion of the QRS sÊ-loop varied considerably because of complicating or multiple infarctions but was generally directed away from the area of infarction.

The configuration and spatial orientation of the remaining portions of the QRS sÊ-loop

were especially influenced by complicating cardiac states, such as right or left ventricular hypertrophy, or conduction defects, such as bundle branch block, but in all the records studied there remained recognizable evidence of all of these complicating states.[6, 7, 12, 13] The duration of the QRS sÊ-loop was increased by left ventricular hypertrophy, probably because of the increased thickness of muscle that the process of depolarization had to traverse. These observations agree with those of investigators who employed other reference frames.[1-5]

The later portions of the QRS sÊ-loop appeared to be deformed by the effect of the areas of infarction upon those processes of depolarization that invade the infarcted myocardial areas later in the electric cycle. These deformities in contour were compatible with a reduction or loss of electric activity in the infarcted areas, resulting in mean instantaneous vectors that were directed away from the infarcted areas or, if directed toward those areas, were reduced in magnitude (figs. 1, 2, 5 and 7). The resultant effect on the QRS sÊ-loop was to appear to remove a section from that portion normally associated with electric activity in the infarcted area within the heart. In figures 1 and 2, for example, an infarct on the diaphragmatic surface of the heart produced arching of the efferent limb of the QRS sÊ-loop. Anatomic and spatial vectorcardiographic correlations in experimental animals and man will be necessary to evaluate this concept adequately, but electrocardiographic and other clinical data, as well as theoretic electrocardiography, seem to support the concept. So far, distortions and alterations in the electrocardiogram correlate well in time and in magnitude with the distortions of the late portion of the QRS sÊ-loop and the areas of infarction. If the electrocardiograms had been recorded at a more rapid film speed, and if the frequency characteristics of the electrocardiograph were satisfactory, the deformities in the QRS complex could also be identified electrocardiographically. The extent remains unknown to which the QRS sÊ-loop and recordings with the specially constructed electrocardiograph may reveal alterations caused by infarction and other localized lesions that modify the order of depolarization late in electric systole. This is a fruitful field for study. Surely, infarcted zones of the myocardium localized to areas that are depolarized late cannot be expected to modify the early portions of the QRS sÊ-loop. Any disturbance other than infarction that interferes with the invasion or the order of depolarization of an area of the myocardium that is depolarized late in the electric cycle may produce deformities late in the QRS sÊ-loop. When all data, including clinical data, are properly considered, fairly reliable differentiations may be made. Further investigation is necessary for proper evaluation of these concepts and problems.

As with the QRS sÊ-loop, the spatial orientations or configurations of J and the T sÊ-loop conformed to the well known principles of electrocardiography.[7, 10-12] J tended to be displaced toward the area of infarction and the T sÊ-loop away from it (fig. 6). The T sÊ-loop tended to be narrow or hairpin in shape and to be oriented away from the infarcted area when infarction was the major lesion. In the presence of severe left ventricular hypertrophy, it tended to be C or horseshoe shaped, a configuration previously described for many spatial vectorcardiograms in left ventricular hypertrophy.

Summary

The electrocardiograms and spatial vectorcardiograms of 20 subjects with anterior myocardial infarction were studied. The early portions of the QRS sÊ-loop were directed away from the area of infarction. Deformities observed in later portions of the QRS sÊ-loop were compatible with loss of manifested electric forces produced by depolarization of areas activated late in the phase of depolarization. This observation is of particular significance because electrocardiograms, as conventionally recorded and interpreted, fail to detect infarcts located in areas of the heart that are depolarized late and that would not be expected to deform the early portions of the QRS complex and QRS sÊ-loop. Although associated changes in time and magnitude

existed late in the QRS complex of the electrocardiogram, their significance would be overlooked in the conventional recording and interpretation.

The junction, J, was spatially oriented toward the area of infarction, whereas the T sÊ-loop was oriented away from the zone of infarction.

Complicating cardiac states, such as right and left ventricular hypertrophy or both, right or left complete bundle branch block and digitalis, tended to alter the spatial vectorcardiogram accordingly. These complicating factors must be considered when the spatial vectorcardiogram is being evaluated. The modifying influence of all of them was recognizable but did not completely camouflage the influences of the infarcts.

Summario in Interlingua

Esseva studiate le electrocardiogrammas e le vectocardiagrammas spatial de 20 patientes con infarcimento myocardial anterior. Le prime portiones del ansa sÊ de QRS habeva un direction abiente ab le area del infarcimento. Deformitates observate in subsequente portiones del ansa sÊ de QRS esseva compatibile con perdita de manifeste fortias electric producite per le dispolarisation de areas a activation plus tarde in le phase de dispolarisation. Iste observation es de signification special proque electrocardiogrammas de registration conventional, interpretate conventionalmente, non detege infarcimentos locate in areas de dispolarisation tardive que non pote causar un deformation del prime portiones del complexo QRS e del ansa sÊ de QRS. Ben que associate alterationes temporal e magnitudinal existeva plus tarde in le complexo de QRS del electrocardiogramma, lor signification non esserea notate per methodos conventional de registration e interpretation.

Le junction J esseva spatialmente orientate verso le area del infarcimento durante que le ansa sÊ de T habeva un direction abiente ab le zona del infarcimento.

Complicationes del stato cardiac—per exemplo hypertrophia dextero—e/o sinistroventricular, bloco complete del branca dextere o sinistre, e digitalis—tendeva a alterar le vectocardiogramma correspondentemente. Tal factores complicatori debe esser prendite in consideration quando on evaluta le vectocardiogramma spatial. Lor influentia modificatori esseva recognoscibile sed non amontava a mascar completemente le influentia del infarcimentos.

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Occlusive Hepatic Venous Catheterization in the Study of the Normal Liver, Cirrhosis of the Liver and Noncirrhotic Portal Hypertension

By W. Jape Taylor, M.D., and J. D. Myers, M.D.

The technic of occlusive venous catheterization has been applied to the liver. The pressure, measured in a small occluded hepatic vein and termed the wedged hepatic venous pressure, correlates well with the portal venous pressure in cats. An elevation of the wedged pressure in man, in the presence of a normal central venous pressure, is diagnostic of cirrhosis. This has proved to be of clinical value in the differentiation of intrahepatic from extrahepatic portal hypertension. The higher wedged hepatic venous pressures in cirrhosis are correlated with the presence of varices or jaundice, but not with the presence of ascites.

THE anatomic location of the portal vein is such that measurements of portal pressure in man have been possible only at laparotomy. The relative inaccessability of the portal vein has been a particular handicap in the study of Laennec's cirrhosis in which the effects of deranged intrahepatic circulation with resultant portal hypertension are of great importance in the course and ultimate outcome of the disease. Various indirect methods[1, 2] for giving an indication of portal pressure have not proved fully satisfactory, and the need for a suitable technique for estimating portal venous pressure has become more pressing with the advent of direct surgical means for attacking the problem of portal hypertension. A method for direct needling of the portal vein in unanesthetized man has recently been reported[3] but its applicability would appear to be limited.

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Occlusive venous catheterization as applied in the pulmonary circuit[4, 5] has proved to be a valuable tool in the study of cardiac physiology and disease. Its application to the hepatic vascular system seemed worthy of trial despite the disadvantage of a dual afferent blood supply to the liver.

In 1951, the technic of occlusive hepatic venous catheterization in man was described[6a and b] with a report of preliminary results in man and in the cat. The present paper provides observations obtained by this method from a group of patients with Laennec's cirrhosis, from a control series of subjects without liver disease, from a number of patients with extrahepatic portal hypertension and from a few patients with congestive heart failure. Data from animals, comparing this occluded hepatic venous pressure with the directly measured portal pressure, are also given. Factors important in assessing the relationship of this pressure to the portal venous pressure are discussed and a correlation of an elevation of the pressure with the complications of cirrhosis is presented.

The pressure obtained in an occluded small hepatic vein was originally termed the hepatic "sinusoidal" pressure with full realization of the anatomic inaccuracy of this name, but with the belief that the pressure gradient between the sinusoids and the occluded vein is small under our experimental circumstances, as discussed later. Friedman and Weiner[7]

arrived separately at this same designation in reporting the use of a similar technique in dogs. Subsequent similar studies in man have been reported by Paton, Reynolds, and Sherlock,[8] by Atkinson and Sherlock,[9] by Krook[10] and by Reynolds and co-workers.[11] Reynolds and his colleagues have designated this occluded pressure the "wedged hepatic vein pressure" and a similar descriptive term is now frequently used in reference to the occluded pulmonary artery pressure. In the interest of uniformity, the name, wedged hepatic venous pressure, will be used throughout this paper.

Methods

In man an open-end venous catheter (usually no. 7 French) is passed with fluoroscopic visualization via an antecubital vein into a right hepatic vein by the usual technique. The catheter is then extended peripherally as far as possible with moderate pressure so as to occlude a small hepatic vein. The exact position varies with the individual subject, but the catheter tip usually appears to lie within 2 to 4 cm. of the lateral abdominal wall (fig. 1). Since fluoroscopy has been done only in the posteroanterior projection, localization in this plane has not been feasible. If much kinking of the catheter in the right atrium is produced in attempting to wedge the catheter peripherally into the hepatic vein, artefacts are produced presumably by the slapping of the catheter with cardiac contractions. These artefacts have a contour suggestive of an arterial pulse wave and were originally believed[6a] to be possibly such waves transmitted through the sinusoidal system. Subsequently, such waves have been recorded almost at will merely by kinking the catheter in various positions in the right atrium.

On withdrawing the catheter into a proximal, large hepatic vein, the operator frequently is aware of an abrupt "giving" sensation indicating that the catheter was well wedged into the small vein. When a catheter is similarly extended into a hepatic vein of an autopsy specimen, it is difficult to keep it in the occlusive position. The "giving" sensation on withdrawal is not present in the dead liver suggesting that in life there may be some muscular contraction of the small vein about the catheter. However, the occluded vascular bed, intravitam, is not in striking spasm as fluid can be readily and without much resistance perfused through the catheter into the occluded vascular bed. Sizeable blood samples can usually be withdrawn using gentle suction. Blood aspirated through the occluding catheter has, in general, the same oxygen content as true hepatic venous blood from that same general area of the liver (tables 2 and 3). When aspiration is too vigorous, the oxygen content of the blood becomes higher than

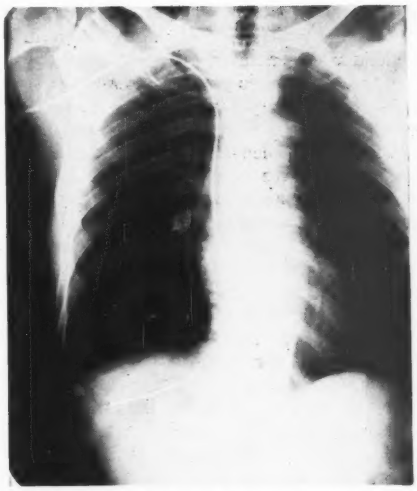

Fig. 1. Roentgenogram demonstrating the usual catheter position for measuring wedged hepatic venous pressure.

that of hepatic venous blood. This is presumably because the blood is drawn so rapidly through the hepatic parenchyma that normal metabolic exchange does not have time to take place.

Pressures were measured with either a Hamilton manometer or with a Lilly electromanometer, using for the baseline a point 5 cm. below the suprasternal notch. Usually the wedged hepatic venous pressure was constant, therefore being recorded as a straight line. When there were significant respiratory variations, mean pressure was determined by integration of the area with a polar planimeter. This latter technic was also used for determination of mean arterial pressure (measured through an inlying needle in a femoral artery) and for atrial pressures. Measurements were made to the nearest 0.5 mm. Hg.

In the individual subject, the wedged hepatic venous pressures measured from different sites in the liver vary by only 1 to 2 mm. Hg. Therefore, when multiple determinations were made, an average figure is given. These small differences make a greater per cent variation in normal subjects, since their pressures are of smaller magnitude. In the study of induced changes in the wedged hepatic venous pressure, it is desirable that the catheter site remains unchanged.

Patients were studied in the postabsorptive state. Usually phenobarbital (90 mg.) had been given orally one hour before the procedure. The study was performed in an air conditioned room. It was accomplished generally without discomfort to the patient and could usually be completed within 30 minutes, except in those cases in which hepatic blood flows and other determinations were subsequently done. In no case has there been any untoward complication.

The group of patients with Laennec's cirrhosis had the usual and typical clinical picture of that disease, in general at a moderately advanced stage. Twenty-five of the 27 cirrhotic patients entered the hospital because of complaints referable to the cirrhosis, (ascites, bleeding varices, jaundice, etc.). In the other two, hepatosplenomegaly and deranged hepatic function, indicative of cirrhosis, were found incidental to study for pulmonary disease. The diagnosis of cirrhosis was confirmed in 17 of the 27 cases by needle biopsy of the liver. Derangement of liver function was severe in all except one case, and that individual was in the group with an hepatic biopsy diagnostic of cirrhosis.

Esophageal and/or gastric varices were considered to be present, if demonstrated by x-ray study, at operation or at autopsy, or if there was a clearcut history of massive hematemesis without other demonstrated cause. The control group was a mixed hospital population of subjects with mild or convalescent illnesses, not expected to produce major hepatic disorders or alteration of portal venous pressure.

Hepatic blood flows were estimated by the bromsulphalein method of Bradley and colleagues[12] with the exception that in many of the cirrhotic subjects, hepatic extraction of bromsulphalein was too poor to permit estimation of hepatic blood flow. In a few of these, blood flow was estimated by the urea technic as previously described[13]; urea concentrations in blood and urine were measured by the colorimetric method of Archibald.[14] Plasma volumes were estimated by the Evans blue method of Gibson and Evans,[15] using a single 10-minute arterial sample after the dye injection. Blood volumes were calculated from plasma volume and hematocrit and the blood volumes were then expressed as per cent of normal, using Gibson's normal values. Oxygen contents of blood samples were determined by the spectrophotometric method of Hickam and Frayser[16] and serum bilirubin by the technic of Mallory and Evelyn.[17] Bromsulphalein excretion is expressed in terms of bromsulphalein (BSP) clearance, as previously defined[18] in per cent of normal clearance.

In animal experiments, cats were anesthetized with pentobarbital, 30 mg. per kilogram intraperitoneally, and a no. 6 French, open-end catheter was placed via the right jugular vein, through the right atrium, occlusively into a small branch of an hepatic vein. A laparotomy was done and a no. 25 hypodermic needle with a hardened plastic extension was placed in the superior mesenteric, portal or splenic vein, with the tip pointing toward the liver. Paired pressures were then recorded from the occluded hepatic vein, via the catheter, and from the portal vein or its tributary within 30 seconds of one another. Since the objective was the comparison of these paired pressures from the two sites rather than their absolute values, the cats were not uniform in regard to fasting, degree of anesthesia, or conditions generally, although most of them remained in a good state throughout the procedure.

Results

Agreement was good between the paired portal venous pressures and the wedged hepatic venous pressures in 18 observations on 10 cats, with the mean wedged pressure being 8.6 mm. Hg and the mean portal venous pressure 8.0 mm. Hg (table 1). This difference is not significant, and the coefficient of correlation is 0.772 ($p < 0.01$). Epinephrine, given directly into the portal vein, produced a rise in the portal venous pressure, but the agreement among 10 paired pressures remained good ($r = 0.663$) ($p < 0.05$), although the wedged hepatic venous pressures were higher than the portal venous pressures to a greater extent than without epinephrine. These points are demonstrated in figure 2 where portal venous pressure is plotted against wedged hepatic venous pressure.

The wedged hepatic venous pressure in each of the 27 cirrhotic patients was higher than the pressure recorded in any one of the group of 18 control patients. In the cirrhotic subjects, the pressures ranged from 11.0 mm. Hg to 50.0 mm. Hg with a mean of 22.3 mm. Hg, while the pressures in the 18 control subjects varied from 0 to 9.5 mm. Hg with a mean value of 5.2 mm. Hg (tables 2 and 3). The difference between the means for the two groups ($p < 0.01$) is highly significant statistically. No correlation exists between the estimated hepatic blood flow and wedged pressure.

There is a significant difference ($p < 0.01$) between the mean hepatic venous pressure in the cirrhotic group as compared with the controls, although no overall difference in the right atrial or femoral arterial pressures were found. The elevated hepatic venous pressure could not be simply correlated with the presence or absence of ascites, probably because of other factors some of which increased intraabdominal pressure while certain others augmented central venous pressure and, thereby, hepatic venous pressure.

Study of the gradient between wedged hepatic venous pressure and central hepatic

TABLE 1.—*Paired Portal Venous and Wedged Hepatic Venous Pressures in Cats*

Cat	No Medication			After Epinephrine		
	Wedged Hepatic Venous Pressure (mm. Hg)	Portal Venous Pressure (mm. Hg)	Difference (mm. Hg)	Wedged Hepatic Venous Pressure (mm. Hg)	Portal Venous Pressure (mm. Hg)	Difference (mm. Hg)
4	13.5	11.0	2.5			
	8.0	7.5	0.5			
	9.0	10.0	−1.0			
7	7.0	7.0	0.0			
	7.0	7.0	0.0			
8	10.5	9.0	1.5			
	11.0	9.0	2.0			
10	6.5	5.0	1.5	16.0	12.5	3.5
	6.0	5.0	1.0			
12	7.0	6.0	1.0	10.0	11.0	−1.0
				9.0	6.0	3.0
				7.0	6.0	1.0
13	10.0	7.5	2.5	15.0	14.0	1.0
	9.0	7.0	2.0	11.5	9.0	2.5
	12.0	13.0	−1.0			
14	6.0	5.5	0.5	11.0	7.5	3.5
				16.0	12.0	4.0
				8.0	7.0	1.0
				14.5	14.0	0.5
15	8.0	9.0	−1.0			
16	7.0	5.0	2.0			
17	8.0	11.5	−3.5			
	10.0	8.5	1.5			
No.	18	18	18	10	10	10
Mean	8.6	8.0	+0.6	11.8	9.9	+1.9
S.D.	2.1	2.3	1.5	3.4	4.1	1.6
S.E.	0.5	0.6	0.4	1.1	1.3	0.5
Range	6.0–13.5	5.0–13.0	−3.5–+2.5	7.0–16.0	6.0–14.0	−1.0–+4.0

venous pressure provides in general much higher gradients in the cirrhotic group than in the control subjects, the mean figure being 16 ± 1.7 versus 1.8 ± 2.1, a highly significant difference. Only one gradient in the control group exceeded 6 mm. Hg (the normal mean of 1.8 mm. Hg plus two standard deviations), this being 7.5 mm. Hg in patient C.B. The reason for this high gradient is not apparent. Only one gradient (3.5 mm. Hg in patient E.G.) in the cirrhotic group fell below a value of 6 mm. Hg. The possible meaning of the low gradient in E.G., who had proven cirrhosis, is discussed later. In general, the wedged-central hepatic venous pressure gradient reflects the wedged pressure alone and computation of the gradient provides no additional diagnostic information.

Figure 3 is a diagrammatic presentation of the wedged hepatic venous pressures in the cirrhotic patients separated into groups, according to the presence or absence of ascites and/or varices in various combinations. It can be seen that most of the higher pressures occurred in

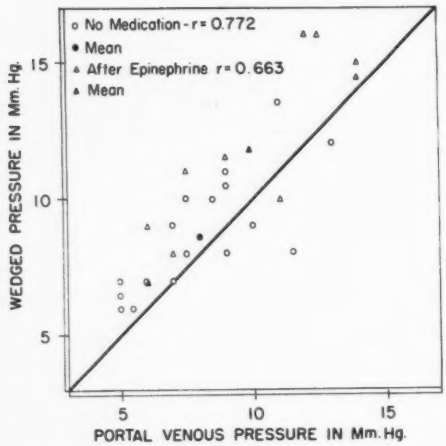

FIG. 2. Relationship of the wedged hepatic venous pressure to portal venous pressure in cats. The heavy line represents absolute agreement of the pressures.

individuals having varices. This association proved to have statistical significance, the difference between the mean pressures of the group with varices and those without varices having a p value of <0.01. The presence of ascites, on the other hand, is not correlated with any significant trend in the wedged pressure, as compared to those individuals who have cirrhosis without ascites.

The blood volume in the group of cirrhotic patients was elevated to a mean value of 17 per cent above normal. The larger blood volumes are, in general, associated with the higher wedged hepatic venous pressures. However, some striking deviations from this are apparent and the coefficient of correlation (r) is only 0.35.

A few of the patients with cirrhosis were moderately jaundiced at the time of the study. This was associated with an exacerbation of their disease and, in general, with very large livers. An arbitrary separation was

TABLE 2.—*Wedged Hepatic Venous Pressure and Related Circulatory Data in Subjects Without Liver Disease*

Subject	Diagnosis	Age Yrs.	Wedged hepatic venous pressure (mm. Hg)	Central hepatic venous pressure (mm. Hg)	Gradient (mm Hg.)	Rt. atrial pressure (mm. Hg)	Mean arterial pressure (mm. Hg)	Estimated hepatic blood flow (ml. min./ sq. M.)	Hemoglobin (Gm. per 100 ml.)	Arterial-wedged hepatic venous oxygen difference (Vol. %)	Arterial-central hepatic venous oxygen difference (Vol. %)	BSP clearance (% normal)	Blood volume (% normal)
JM	Psychoneurosis	34	0.0	0.0	0.0		64	580	13.7		5.4	90	+13
PW	Psychoneurosis	58	2.0	1.0	1.0			620	13.3		4.2	85	−1
SL	Psychoneurosis	51	6.0	4.0	2.0		86	580	15.8		5.6	81	−2
RA	Psychoneurosis	34	3.0	2.0	1.0		77	550	15.9		5.9	105	+16
CB	Psychoneurosis	44	9.5	2.0	7.5	2.0	70	650	13.6		4.6	96	+8
NR	Duodenal ulcer	50	6.0	5.0	1.0	5.0	81	1050	14.8	4.1	4.7	105	−7
JW	Duodenal ulcer	42	8.0	2.5	5.5	2.5	106	650	15.9	4.9	6.0	93	+14
HB	Acromegaly	28	8.0	5.0	3.0			640	14.4		4.9	88	−10
AD	Gastritis	30	6.0	7.0	−1.0	0.0	80	840	10.1		4.1	110	−13
DC	Arthritis	35	8.0	4.5	3.5	3.0	71	1230	9.4		2.2	93	+18
GW	R. arthritis	51	4.0	3.0	1.0		99	740	11.6		4.0	85	+15
HS	Psychoneurosis	42	5.5	6.0	−0.5		65	750	12.6		3.7	70	−4
FW	Duodenal ulcer	38	4.5	3.5	1.0	4.5	81		12.9	3.1	4.0		
GM	CNS syphilis	37	8.5	6.5	2.0	5.0							
GW	Duodenal ulcer	58	5.0	2.5	2.5	1.5	80	530	14.9		6.1	85	−11
IJ	Duodenal ulcer	40	7.0	5.0	2.0				9.4		4.5		−13
WY	CNS degeneration	64	1.0	1.0	0.0	−1.0	102	820	11.7		3.9	71	−5
JA	Malnutrition	37	1.0	1.0	0.0		60	810	9.8		3.9	78	−9
No.			18	18	18	9	14	15	17		17	15	16
Mean			5.2	3.4	1.8	2.5	80.1	736	12.9		4.6	89.0	+5.3
S.D.			2.4	2.1	2.1	2.1	14.2	194	3.4		1.0	11.8	10.0
S.E.			0.6	0.5	0.5	0.7	3.8	50	0.8		0.2	3.1	2.5

TABLE 3.—*Wedged Hepatic Venous Pressure and Related Circulatory Data in Patients with Laennec's Cirrhosis*

Subject	Age Yrs.	Wedged hepatic venous pressure (mm. Hg)	Central hepatic venous pressure (mm. Hg)	Gradient (mm. Hg)	Rt. atrial pressure (mm. Hg)	Mean arterial pressure (mm. Hg)	Estimated hepatic blood flow (ml./min./sq. M.)	Hemoglobin (Gm. per 100 ml.)	Arterial-wedged hepatic venous oxygen difference (Vol. %)	Arterial-central hepatic venous oxygen difference (Vol. %)	BSP clearance (% of normal)	Ascites	Esophageal varices	Serum bilirubin (mg. per 100 ml.)	Blood volume (% of normal)
TP	44	32.0	3.0	29.0	3.5	63	770*	13.9		3.5		+	+	9.3	+34
EH	45	17.0	10.0	7.0	0.0	65		10.5	6.5	6.6	16	+	+	2.1	+18
MM	54	15.0	2.5	12.5	0.0	94	420*	11.4		4.2	31	+	−	2.0	+18
WE	51	26.0	5.0	21.0	0.5	87		10.8		4.7		−	+	<1.0	−42
EG	40	11.5	8.0	3.5	7.0		850†	10.3			89†	−	+	<1.0	+7
LD	48	15.5	5.0	10.5	2.0	119	890	13.6		4.2	62	−	−	<1.0	+2
BD	54	23.5	6.0	17.5	0.0	99		13.0	4.2	4.9		+	+	1.2	−1
WG	49	25.0	6.5	18.5	5.0	100		8.1	2.2	2.3		+	+	4.5	+34
JP	32	37.0	14.0	23.0	0.0		920*	11.0		4.0		+	+	7.5	+47
JP	32	18.5				86		11.8	2.5	3.0		−	+	<1.0	+13
RB	49	12.0	2.5	9.5	4.0	76		11.1		4.2	31	−	−	1.6	+9
AW	60	19.0	6.0	13.0	2.0	67	410	11.1	5.5	7.4	27	+	+	1.4	−3
HB	51	30.0	6.5	23.5	5.0	86		13.9	4.2	3.6	22	+	+	2.2	+28
HB	51	27.0	9.5	17.5				12.1		3.5	42	+	+	2.7	+15
AS	61	22.0	6.0	16.0	0.0	84	590	11.1	6.5	8.3	28	+	+	1.8	+59
RS	66	18.0	5.5	12.5	3.5			9.8	5.9	6.0	25	+	−	1.5	+9
EP	34	14.0	5.0	9.0	5.0	94		10.5		4.1	52	+	−	1.5	+9
EJ	66	21.0	7.5	13.5	6.0	102		8.8		8.2	24	+	−	<1.0	−8
JB	53	20.0	4.0	16.0	3.5	83		13.1	3.1	2.9	27	+	−	3.4	+40
WJ	36	23.0	4.5	18.5	8.0	82		9.4	2.8	2.8		−	−	8.2	+41
MB	32	20.0	9.5	10.5	10.5	68		11.8	3.7	5.2		−	+	2.1	+6
NS	39	28.0	8.0	20.0	3.0	78	930	10.2	4.4	4.2	44	+	+	<1.0	+3
LB	44	38.0	7.0	31.0	4.5	78		9.0		3.1	31	−	+	3.7	+16
WD	40	25.0	4.5	20.5	3.5	96		11.2		7.3		−	+	<1.0	−7
HH	40	17.0	10.0	7.0				11.0		4.8	26	−	+	1.3	+2
WP	36	15.0	9.0	6.0	4.0	86		10.3		4.5	15	+	−	7.2	+17
JP	29	16.0	6.5	9.5	3.5	85	690	11.1		5.7	49	−	+	1.5	+22
MM	35	11.0	2.0	9.0	0.5	85		12.2	3.6	4.9		+	−	2.5	
BS‡	18	50.0	5.0	45.0	2.0	72	340	8.5		5.6	36	−	−	1.2	+14
No.		29	28	28	26	24		29	13	28	19				28
Mean		22.3	6.4	16.1	3.1	85		10.8	4.2	4.8	36				+17
S.D.		6.5	2.0	8.9	3.0	13		1.5	1.5	1.6	18				17
S.E.		1.2	0.4	1.7	0.6	3		0.3	0.4	0.3	4				3

* Hepatic blood flow estimated by urea method.

† Determinations made one year previously.

‡ Post-necrotic cirrhosis. Not used in statistical analysis of complications of cirrhosis. See text.

made between those patients with total serum bilirubin greater than 3.0 mg. per 100 cc. and those with less than 3.0 mg. per 100 cc., since this division seemed to fit best with a clinical separation of these two groups. The more deeply jaundiced patients had much higher pressures than the nonjaundiced or lightly jaundiced patients, the mean pressures being 27.1 mm. Hg and 19.3 mm. Hg, respectively ($p < 0.01$). In the statistical analysis which correlates pressures with the complications of cirrhosis, the last patient (B.S.) is omitted because he clearly represented a unique circumstance, as is subsequently discussed.

Table 4 summarizes 11 observations on 10 patients with portal hypertension clinically who eventually proved not to have hepatic cirrhosis. Five of these, who had hemorrhaged from esophageal varices, were thought to have cirrhosis on clinical grounds, but in all five wedged hepatic venous pressures were normal and all five subsequently had normal

liver biopsies. In the five other patients with the syndrome of portal hypertension (four with esophageal varices and one with ascites and splenomegaly), clinical evidence provided a diagnosis of portal hypertension of extrahepatic cause. Again, all five had normal

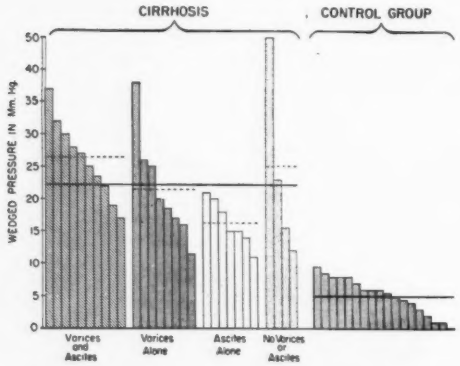

FIG. 3. The wedged hepatic venous pressure in Laennec's cirrhosis and in normal subjects. The horizontal line across each group represents the mean pressure for that group.

wedged hepatic venous pressures and no cirrhosis was demonstrated by liver biopsy. Laparotomy in 8 of the above 10 patients confirmed the presence of extensive portal venous collaterals, and direct pressure measurements in peripheral branches of the portal venous system demonstrated portal hypertension in all eight.

Measurements of the wedged hepatic venous pressure were made in four patients with congestive heart failure of diverse etiology. The mean right atrial pressure in this group was 14.5 mm. Hg and the central hepatic venous and wedged hepatic vein pressures 14.5 and 15.0 mm. Hg, respectively. These data, (table 5) are in agreement with those of Krook,[10] and Paton, Reynolds and Sherlock,[8] demonstrating that an elevation in central venous (i.e., right atrial), pressure is accompanied by a comparable increase in central hepatic venous and wedged hepatic venous pressures. There is no elevation of the gradient between wedged pressure and the central hepatic venous pressure.

TABLE 4.—*Wedged Hepatic Venous Pressure and Related Circulatory Data in Patients with Extrahepatic Portal Hypertension*

Subject	Etiology of portal hypertension	Age Yrs.	Wedged hepatic venous pressure (mm. Hg)	Central hepatic venous pressure (mm. Hg)	Gradient (mm. Hg)	Rt. atrial pressure (mm. Hg)	Mean arterial pressure (mm. Hg)	Estimated hepatic blood flow (ml./min./sq. M.)	Hemoglobin (Gm./100 ml.)	Arterial-wedged hepatic venous oxygen difference (Vol. %)	Arterial-central hepatic venous oxygen difference (Vol. %)	BSP Clearance (% normal)	Blood volume (% normal)
SP	Unknown	15	5.0	4.0	1.0		94		8.3		6.1		
PC	Pseudocyst of pancreas	32	8.5	3.5	5.0	2.5	80	870	11.9		5.3	88	+12
LF	Unknown	43	8.0	9.0	−1.0	7.0	146	390	10.7	7.7	6.8	34	+38
WM	Thrombosis of portal vein	30	7.5	3.5	4.0	5.0	93	820	9.0	1.9	4.2	72	+9
FW	Unknown	43	8.5	6.5	2.0	5.5	76	830	9.7	5.1	5.3	40	0
TB	Cavernous transformation	17	5.5	2.0	3.5	4.0	78	520	11.3	3.1	4.0	85	−6
GM	Unknown	51	4.0	3.5	0.5	2.5	95	500	12.1		5.3	69	+6
GM	Unknown	52	2.5	−1.0	3.5			460	10.5		4.8	51	+26
BM	Unknown	10	8.0	4.0	4.0	5.0	76	1050	8.5		3.8	95	−1
EA	Unknown	49	9.5	4.5	5.0	2.5		470	11.1		5.7	64	−19
KL	Unknown	42	4.0	1.0	3.0	−1.0		660	10.6		3.8	78	+21
No.			11	11	11	9	8	10	11		11	10	10
Mean			6.5	3.7	2.8	3.7	72	657	10.3		5.0	68	9
S.D.			2.4	2.6	1.9	2.3	23	70	1.3		1.0	21	17
S.E.			0.7	0.8	0.6	0.8	8	22	0.4		0.3	7	5

TABLE 5.—*Wedged Hepatic Venous and Central Venous Pressures in Heart Failure*

Patient	Age (Yrs.)	Diagnosis	Wedged hepatic venous pressure (mm. Hg)	Central hepatic venous pressure (mm. Hg)	Gradient (mm. Hg)	Right atrial pressure (mm. Hg)	Mean arterial pressure (mm. Hg)	Arterial-central hepatic venous oxygen difference (vol. %)
W. W.	28	Rheumatic ht. disease	18.0	14.0	4.0	14.5	65	7.6
P. I.	48	Unknown	15.0	15.5	−0.5	14.5		5.5
R. C.	11	Congenital ht. disease	10.0	12.0	−2.0	12.0	83	6.2
L. W.	50	Myxedema ht. disease	17.0	16.5	0.5	17.0	80	8.4
No.			4	4	4	4	3	
Mean			15.0	14.5	0.5	14.5	76	
S.D.			3.6	1.9	2.6	2.0	8	
S.E.			1.8	1.0	1.3	1.0	4	

DISCUSSION

The first point for discussion must be the relationship of the wedged hepatic venous pressure, as herein measured, to the actual portal venous pressure. The most important considerations regarding this relationship are to be found in the experiences which directly relate the wedged pressure to portal venous pressure.

The good agreement in the cats, both before and after epinephrine, between wedged hepatic venous and portal venous pressures would indicate that in this species, portal venous pressure can be predicted from wedged venous pressure. Friedman and Weiner[7] found the same close relationship between the two pressures to exist in the dog also. The somewhat higher level of wedged hepatic venous pressure as compared with portal pressure in the cats may be due to the fact that the dynamic component of the vascular pressure, so-called end-pressure, is subtracted from the portal venous pressure where the needle lay in the direction of flow.

Paton, Reynolds and Sherlock[8] and Reynolds and associates[11] have made direct comparisons of the portal venous pressure and occluded hepatic venous pressure in man. Both groups report good agreement between these pressures in normal subjects and in patients with Laennec's cirrhosis. Reynolds and his associates found the wedged hepatic venous pressure to be consistently lower (average 20 per cent) than the simultaneously measured portal venous pressure in cirrhotic patients, but found no large discrepancy in any individual study. In their simultaneous pressure measurements the catheter had been positioned before the patients were taken to the operating room and the original placement may not have been maintained; anesthesia could conceivably interfere with the tightness of the wedging. These authors found the wedged hepatic venous pressure lower at operation than when measured pre-operatively and tentatively ascribed this difference to a decrease in hepatic blood flow. However, their most significant point is the very significant correlation between the occluded hepatic venous pressure and the portal venous pressure.

Many investigators, including Walker,[19] Rousselot,[20] Bellis[21] and Taylor and Egbert[22] have measured portal venous pressure at laparotomy on humans with normal livers. Results are variable but an average pressure of about 13 mm. Hg is reported. It should be noted, however, that Walker,[19] in a recent report gives the normal range of portal venous pressure at from 6 to 11 mm. Hg, more in keeping with our observed wedged hepatic venous pressures. Part of the discrepancy in portal venous pressure among the various surgical observers may be due to the use of inconstant baselines from which to measure the pressure. It should not be forgotten that all of these measurements are on operated man under anesthesia and may not represent the physiologic situation in the intact human. We must allow, on the other hand, that our observed wedged hepatic venous pressures in

normal persons may be less than the true portal venous pressure, possibly because of the richness of the anastomotic runoff, although the observations of Paton and coworkers[8] do not support such a discrepancy.

Direct measurements of portal venous pressure in cirrhotic subjects have also been made[21-24] at laparotomy. It is of note that such pressures are of the same general magnitude as the wedged hepatic venous pressures of the present cirrhotic group.

Two factors are of paramount importance in considering the relationship of the wedged hepatic venous pressure to portal venous pressure: (1) the influence of the hepatic arterial pressure on the total afferent blood pressure to the liver and (2) the collateral circulation within the liver, which determines the degree to which the wedged catheter obstructs blood flow.

It is apparent that the hepatic arterial pressure and the portal venous pressure must come into equilibrium at the point where the two systems merge or there could be no portal venous flow. Thus one may look upon the two afferent hepatic pressures, portal venous and arteriolar, as being in equilibrium in the proximal, i.e., more portal areas of the sinusoidal bed.

The next consideration, therefore, must be the pressure gradient between this proximal portion of the sinusoidal bed and the occluded hepatic vein. In the normal liver the pressure in the obstructed area will just barely exceed that in the neighboring unobstructed areas because of the richness of the sinusoidal anastomoses[25] and the interconnections from one small hepatic vein to another[26], i.e., between hepatic veins smaller than that which the catheter occludes. The measured wedged hepatic venous pressure can be lower than the true afferent pressure (portal venous and hepatic arteriolar pressures in equilibrium) but by no more than the pressure gradient across the sinusoids and their anastomoses. Since this gradient is normally quite small, the sinusoidal bed being a low resistance system, the wedged hepatic venous pressure approximates the true portal venous pressure in the normal liver. That this is a low resistance system has been established by the observations of others[27-29] as well as ourselves that postmortem perfusion of the liver through the portal vein is easily accomplished in large volume at low pressure. Furthermore, we have found that reverse perfusion through the hepatic vein with the portal vein as efferent is about as easily accomplished.

In cirrhosis of the liver, the fibrous disorganization of the hepatic architecture and vasculature[28] reduces significantly the intersinusoidal and intervenous anastomoses from one hepatic segment to another. If the anastomotic channels are very severely constricted, it might be expected that the pressure in the occluded hepatic vein would of necessity approach hepatic arterial pressure. In actuality the wedged hepatic venous pressure in cirrhosis rises approximately to the portal venous pressure and further rise is prevented by dissipation of pressure into such collateral channels as are still present within the liver, as, for example, the portal venous to hepatic venous communications demonstrated by Popper and associates.[30] Furthermore, the large volume portal venous bed with its extrahepatic collaterals does not allow any rise of the wedged hepatic venous pressure above the portal venous pressure.

In some circumstances, however, the wedged hepatic venous pressure does not give a true estimate of portal venous pressure in cirrhosis. The last cirrhotic patient, (B.S.), with "postnecrotic" scarring, had a liver estimated to be one fifth of normal size at laparotomy and a portal venogram demonstrated that the portal vein was patent up to the liver, although occlusion of the portal vein within the liver could not be excluded. Such large collateral veins were present that a more effective portacaval shunt could not have been produced surgically. The wedged hepatic venous pressure, which had been measured previously, was 50 mm. Hg, greatly exceeding the directly measured portal venous pressure of 15 mm. Hg. The hepatic blood flow was reduced to 340 ml. per minute per square meter of surface area, which very likely indicates a greatly diminished portal venous flow through the liver. Instances of

portal collaterals without portal hypertension are rare, however,[31-33] and it remains our opinion that in the great majority of cases of inoperated cirrhosis the wedged pressure reflects with remarkable accuracy the elevated portal venous pressure.

It was the hope preliminarily that repeated measurements of wedged hepatic venous pressure would be useful in the postoperative evaluation of various surgical procedures for portal hypertension of cirrhotic origin. However, studies[34] thus far indicate that, in severe cirrhosis associated with portal hypertension, the wedged pressure remains high after complete diversion of portal venous blood from the liver through an end-to-side portacaval anastomosis. This is interpreted to mean that in advanced cirrhosis the obstruction to flow is so marked that a high intrasinusoidal pressure is provided by the hepatic arterial afferent alone. Under such circumstances the wedged pressure cannot, of course, reflect portal venous pressure nor can it give any idea of the efficacy of the portacaval shunt in reducing portal venous pressure.

That the wedged hepatic venous pressure does ordinarily give a good estimate of portal venous pressure in cirrhosis indicates that the vascular obstruction in cirrhosis is either sinusoidal or postsinusoidal. If the obstruction were presinusoidal, the wedged pressure would be much lower than the portal pressure.

A secondary factor, the intra-abdominal pressure, would be expected to affect the wedged hepatic venous pressure. In our studies, no measurements of intraabdominal pressure have been made. However, it would be expected to affect the wedged pressure and central hepatic venous pressure alike; thus, there would be no effect on the wedged-central hepatic venous pressure gradient, which would remain small in the normal person and high in subjects with cirrhosis. The clinical and diagnostic significance of a high wedged hepatic venous pressure would not be masked by an increase in intra-abdominal pressure. Likewise, any influence which elevates the systemic central venous pressure raises the wedged hepatic venous and portal venous pressures concomitantly, and the gradient is not disturbed. This is best illustrated by congestive heart failure where the wedged hepatic venous pressure is elevated but only by an increment equal to the increase in systemic venous (including central hepatic venous) pressure.

Although some of the theoretic aspects are not subject to direct proof, the practical usefulness of occlusive hepatic venous catheterization seems well established. The separation of the high pressures in Laennec's cirrhosis from the low pressures in patients without advanced liver disease has been absolute to the point that an elevation of the wedged hepatic venous pressure has been useful in differential diagnosis. A special corollary of this ability to distinguish cirrhosis is the separation of cirrhotic from noncirrhotic (extrahepatic) portal hypertension. Frequently, this differentiation is of crucial importance in planning surgical treatment for portal hypertension and, at times, a correct decision may be made by other means only with considerable difficulty. To date, the accuracy of the wedged hepatic venous pressure in separating the portal hypertension of cirrhotic from that of noncirrhotic etiology has been absolute.

The fact that the wedged hepatic venous pressure is no higher in cirrhotics with ascites than in those without it is further evidence that an increased portal pressure, per se, is not the determining factor in ascites formation.[35-37]

Esophageal varices are generally believed to be a result of increased portal venous pressure. The difficulty in relating the observations herein reported to the pathogenesis of varices is that the varices are already present when the study is made and the portal pressure may have been quite different during the development of the varices. An example of this is seen in the patient, J. P., whose wedged hepatic venous pressure changed from 37 to 20 mm. Hg over a period of several months of medical therapy, during this time, ascites and jaundice disappeared, liver function improved, and his liver decreased in size. However, varices persisted and even bled at this later time. Nevertheless, as pointed out earlier, the demonstration of higher wedged pressures in

the group of patients with cirrhosis and varices, than in those having cirrhosis but without varices, supports the view that the level of the portal pressure is important in the formation of varices. It is well known clinically and recently reemphasized by Walker[19] that the correlation of the degree of elevation of portal venous pressure and the intensity of the cirrhotic process by pathologic criteria is by no means close. Patient E. G. in the present series is a striking example of such a discrepancy. This patient, who had extensive esophageal varices and repeated massive hematemeses, had the lowest wedged hepatic venous pressure in the entire cirrhotic group. His cirrhosis had been proven by biopsy, but he had a normal bromsulphalein clearance one year previous to the pressure measurements and a normal routine 45-minute bromsulphalein test at the time of the study. The explanation for his relatively low pressure is not clear. It is possible that a recent severe hemorrhage had reduced his portal venous and wedged hepatic venous pressures, or that some extrahepatic factor, such as a portal venous thrombus, influenced the formation of varices without much rise in intrahepatic vascular pressure.

Noteworthy is the correlation in liver disease of a higher wedged hepatic venous pressure with the presence of jaundice. Each of the cirrhotic patients who was jaundiced had a very large liver which was presumably due in part to fatty metamorphosis (this was demonstrated microscopically in some instances). It seems reasonable that intrahepatic obstruction under these circumstances would be greater, producing a higher portal pressure. This is in line with Dock's observation[29] on the decreased perfusability of a large fatty liver.

The correlation between increased wedged hepatic venous pressure and an elevated blood volume in some instances of Laennec's cirrhosis is interesting, but not unexpected, since a similar volume-pressure relationship exists in the vascular system under other conditions.[38, 39] The meaning of this correlation is, however, difficult to ascertain. It is conceivable that the increased blood volume contributes to an increased pressure analogous to the changes found in a distended closed section of vein and in the pulmonary circuit. In many instances, the greatly dilated portal venous bed would seem to accumulate the increment in blood volume without per se producing portal hypertension. The most likely explanation of the volume-pressure relationship seems to be that they are not causally related, but merely coexisting manifestations of a severe stage of the same disease.

Summary

1. The technic of occlusive venous catheterization of the liver in man is described.

2. The pressure obtained in an occluded small hepatic vein has been termed the wedged hepatic venous pressure.

3. In cats, the wedged hepatic venous pressure and portal venous pressure are essentially the same.

4. In 29 observations on 27 patients with Laennec's cirrhosis, the wedged hepatic venous pressure has, in each instance, been higher than any observation in 18 control subjects, thus establishing diagnostic significance for an elevated pressure.

5. The procedure has been of practical value in the separation of cirrhotic from noncirrhotic (extrahepatic) portal hypertension.

6. The wedged hepatic venous pressure is particularly high in those cirrhotic subjects with esophageal varices and with jaundice, but the degree of elevation cannot be correlated with the presence or absence of ascites.

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Summario in Interlingua

Le technica del occlusive catheterisation venose esseva applicate al hepate. Le pression mesurate in un occludite minor vena hepatic (designate como le "cuneate pression hepatovenose") se monstrava ben correlationate con le pression del vena portal in cattos. In homines, un elevate pression cuneate in association

on un normal pression venose central es agnostic pro cirrhosis. Iste facto se ha rovate de valor in le differentiation de intra- epatic e extrahepatic hypertension portal. Le ius alte cuneate pressiones venose hepatic ue occurre in cirrhosis es correlationate con presentia de varices o ictero sed non de scites.

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Concealed Conduction

Further Evaluation of a Fundamental Aspect of Propagation of the Cardiac Impulse

By RICHARD LANGENDORF, M.D., AND ALFRED PICK, M.D.

Recognition of concealed conduction of the cardiac impulse is shown to be indispensable for the understanding of many cardiac arrhythmias. After a historical review of the concept of concealed conduction, records are presented to demonstrate established, as well as hitherto undescribed, aspects of concealed A-V conduction. Then, the manifestations of concealed intraventricular conduction are pointed out and, finally, the relationship of the phase of concealed conduction to the supernormal phase is discussed.

THE earliest phase of the relative refractory period of the specific conduction system is characterized by a partial response to the cardiac impulse, inasmuch as the impulse penetrates into the conducting tissues but fails to traverse them completely. This concept, based upon experimental evidence, was clearly enunciated by Engelmann[1] and Erlanger.[2] However, its precise mechanism was investigated only much later by Ashman and Herrmann,[3-5] Drury and Lewis,[6, 7] and Lewis and Master.[8] Scherf and Shookhoff,[9] studying the effect of premature beats upon A-V nodal rhythm, postulated a penetration of nonconducted impulses into the A-V junction. Kaufmann and Rothberger[10] and Wenckebach and Winterberg[11] were aware of the significance of such abortive penetration of the cardiac impulse and considered it in analyzing arrhythmias of the human heart. Winternitz[12] and, independently, Luten and Jensen[13] were the first to point out the disturbance of impulse formation in the A-V node as a result of partial conduction of sinus impulses in cases of incomplete A-V dissociation engendered by acceleration of a subsidiary pacemaker. Winternitz and Langendorf[14] demonstrated that penetration of "blocked" sinus impulses has to be postulated to explain the variations of retrograde conduction in cases of A-V block with V-A response. In a previous report from this department[15] the term *concealed conduction* was introduced and the various manifestations of the phenomenon pertaining to A-V conduction were described.

Concealed conduction of the cardiac impulse is manifested by its after-effects, involving either the *conduction or formation of a subsequent impulse*. In the former case, impulse conduction is unexpectedly delayed or stopped; this is due to the creation of refractoriness in conduction pathways by penetration of the preceding "blocked" impulse. In the latter case, discharge of an expected subsidiary impulse is delayed or fails to occur; this is due to premature extraneous discharge of a subsidiary pacemaker located in the path of the penetrating "blocked" impulse.

Since we have focused our attention on these two manifestations of concealed conduction in the human heart, the concept proved extremely valuable in providing the key to the understanding of various otherwise unexplainable features of simple and complex arrhythmias. It has been utilized by us and others in the interpretation of conduction disturbances engendered by premature systoles[16-18]; of apparent irregularities of the nodal pacemaker in A-V dissociation with or without A-V block[19-23]; to unravel satisfactorily irregularities of auricular and ventricular beating in complex arrhythmias, such as A-V nodal tachycardia with unequal degrees

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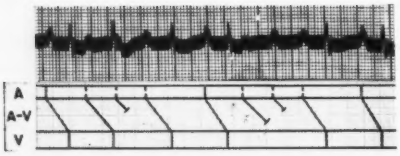

FIG. 1. Concealed A-V conduction in a case of A-V block causing blockage of two consecutive auricular premature systoles. The conventions in the diagram are: A-V represents the spread of the impulse through the A-V junction between the auricles (A) and the ventricles (V); oblique lines at different angles indicate varying speed of impulse conduction; the short lines at right angles to the oblique lines indicate stoppage of the impulses; varying length of the oblique lines representing such stopped impulses indicates the varying distance to which the impulses penetrate into the A-V junction.

Two types of P waves are seen: one, tall and peaked (the first, fifth and last), represents sinus impulses conducted to the ventricles at a prolonged P-R interval of 0.28 second, indicating depression of A-V conductivity. The other, smaller and notched (the second to fourth, and the sixth to eighth), represents runs of three successive auricular premature systoles at a rate of 167. Transmission of these ectopic impulses to the ventricles is irregular. In the first group, the first and last is conducted at a P-R of 0.30 second and the middle one is blocked. In the other group, the first two are blocked and the last is conducted at a P-R of 0.30 second.

The cause for this apparently different response of the A-V junction to the rapid stimulation by the two identical triads of ectopic impulses is indicated in the diagram. In both groups the first of the ectopic impulses penetrated into the A-V junction. In the first group it traversed it and reached the ventricles, in the other it failed to do so. Evidently, its deep penetration created refractoriness in the traversed part of the junction of sufficient degree so as to prevent the transmission of the subsequent ectopic impulse in the same way as in the first group. Its partial *conduction* is *concealed* and revealed only by the otherwise unexplained failure of the next ectopic impulse to pass. Thus, both triads of ectopic beats actually yield a similar 2:1 response of the A-V junctional tissue: in the first triad this response was complete, in the other incomplete, simulating a 3:1 response.

The cause of success or failure of the ectopic impulses in traversing the A-V junction is revealed by close examination of their R-P intervals. The first premature P wave of the second triad occurred 0.2 second earlier than that of the first triad. Evidently, here the impulse reached the A-V junction at the transition of the absolute into the relative refractory phase, during the *phase of concealed conduction*.

of forward and retrograde block,[24] or in an unusual case of ventricular parasystole complicating A-V dissociation.[25] The concept proved indispensable for the understanding of the ventricular response in certain cases of auricular flutter[26] and probably also in auricular fibrillation,[27, 28] for the interpretation of some cases of reciprocal beating[22, 29-31] and for the explanation of the failure of A-V nodal escapes to occur at the expected time in cases of auricular fibrillation.[32] Failure to recognize the operation of concealed A-V conduction in cases of second degree A-V block has led, in our opinion, to erroneous interpretations and unwarranted deductions.[33-35]

The purpose of the present report is: (1) to demonstrate the usefulness of the concept of concealed conduction in explaining certain aspects of impaired A-V conduction in sinus as well as ectopic rhythms, in particular multiple successive blockage of auricular impulses and the failure of A-V nodal escapes to appear during long ventricular pauses; (2) to point out the different mechanism of blockage of successive auricular impulses in auricular flutter or tachycardia associated with group beating of the ventricles; (3) to discuss possible applications of the concept of concealed conduction to the analysis of disturbances of intraventricular conduction, to the interpretation of some peculiarities of the pre-excitation syndrome, and to the understanding of the timing of ventricular premature systoles; and (4) to examine the relationship between the supernormal phase and concealed conduction in the A-V junction.

MATERIAL

The material of this report comprises nine records obtained on six patients and illustrates: (1) runs of auricular premature systoles revealing the operation of concealed conduction responsible for blockage of two consecutive impulses and elucidating the mechanism of 3:1 A-V response (fig. 1); (2) incomplete A-V dissociation (without A-V block), in which the occurrence of "abortive" ventricular captures, permits determination in the human heart of the part of the cycle occupied by the phase of concealed conduction (fig. 2); (3) second degree A-V block (involving two levels of the A-V junction) with seemingly irregular discharge of the escaping A-V nodal pacemaker, clarified by the demonstration of concealed conduction (fig. 3); (4) second

egree A-V block with unusually long ventricular auses, with or without nodal escape, likewise larified by implication of repetitive concealed conuction, which causes multiple blockage of consecuive auricular impulses as well as multiple consecuive discharge of the subsidiary (A-V nodal) pacemaker (figs. 4, 5 and 6); (5) successive blockage of uricular impulses in auricular flutter with irregular -V conduction and group beating of the ventricles s a result of varying penetration of the A-V junction y flutter impulses due to two areas of conduction mpedance (fig. 7); and finally, (6) auricular tachyardia with group beating (bigeminy) of the ventrilles as a result of either of the two mechanisms—two egions of impedance or concealed conduction in the -V junction (fig. 8*A* and *B*).*

The analysis of all electrocardiograms is presented n diagrammatic form and is fully discussed in the espective legends. The conclusions drawn from the nterpretation of these records form the basis for the ollowing comment.

Comment

The portion of the cardiac cycle at the transition of the absolute into the relative refractory phase, during which partial (concealed) penetration of the impulse into the conduction pathways takes place, was termed by Lewis and Master[8] the "phase of interference." We propose to name it the *phase of concealed conduction* in order to avoid confusion with the term interference used in a different and wider sense.[28] Such a phase of concealed conduction can be demonstrated with normal as well as depressed conductivity (figs. 2 and 3). However, it is not always possible to delineate sharply the time it occupies within the cycle,[17] as was possible in figure 2. In constructing recovery curves of conductivity in such cases, the effect of cycle length upon refractory period must be taken into consideration in addition to the simple determination of R-P and P-R relationships, customarily used for this purpose; and this is true, not only for completed but also for partial (concealed) conduction.[5, 26] Nevertheless, it would appear that the phase of concealed conduction may lengthen, if conductivity is depressed, just as is the case with the absolute and relative refractory phases.

Concealed A-V conduction should not be viewed as an exceptional phenomenon that is helpful in unraveling rare and complex arrhythmias only. Actually, one of its manifestations, namely, the effect on *conduction of a subsequent impulse* has to be invoked to account for the consequences of the most trivial disturbance of cardiac rhythm, that is, ventricular premature systoles.[15] Here, concealed retrograde spread of the ectopic impulse into the A-V junction is the cause for the occurrence in sinus rhythm of a compensatory pause, or of a prolonged A-V conduction time subsequent to interpolation of the ectopic beats, and in auricular fibrillation for the pauses, following ventricular premature systoles.[36, 37] A less common, but more obvious manifestation of concealed conduction in ectopic impulse formation is the occurrence of unexpected disturbances of A-V conduction during runs of auricular premature systoles, exemplified in figure 1. Under all these circumstances, each concealed conduction of an impulse sets up physiologic refractoriness of A-V junctional tissue, delaying or preventing transmission of a subsequent impulse. Such mechanisms operating in conjunction with depressed A-V conductivity, for example in second degree A-V block, are illustrated in figures 4, 5 and 6 and in figure 8. As a rule the presence of concealed A-V conduction in such records can be considered proven, when in some portions of the same record completed (but delayed) conduction of auricular impulses is seen under comparable conditions, that is, with identical or almost identical R-P intervals.

The other manifestation of concealed conduction is a disturbance it causes in the regularity of *impulse formation* in a subsidiary pacemaker. This is usually seen in cases with A-V dissociation with first degree A-V block[19] but may occur as a physiologic phenomenon in the absence of impairment of A-V conductivity.[21] An instance of the latter variety is illustrated in figure 2. Detailed analysis of this case, as indicated in the legend and applied to the entire material available, permitted determination of the duration of the phase of concealed conduction, that is, that

* We are indebted to Dr. S. K. Wilhelm for his kind permission to use the material of figure 8.

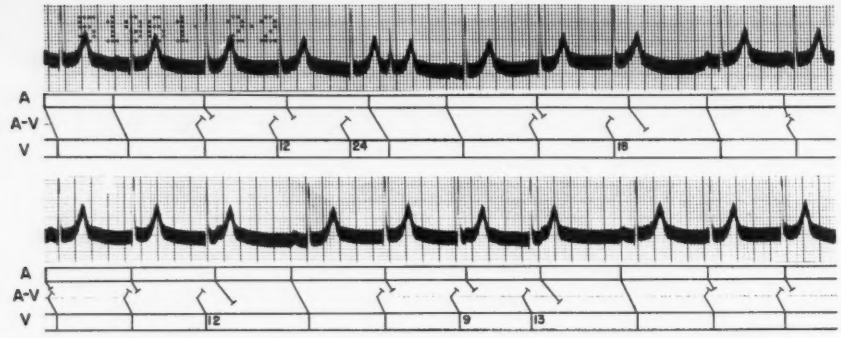

FIG. 2. Incomplete A-V dissociation (without A-V block) with successful and attempted ventricular captures. The duration of the phase of concealed conduction in the absence of A-V block. The two strips shown are a continuous portion of a long lead II, the last beat of the upper strip is reproduced as the first of the lower strip. The conventions in the diagram are the same as in figure 1. Impulses arising in the A-V node, spreading towards the ventricles, and in retrograde fashion towards the auricles, are indicated by oblique lines originating in the center of the A-V node. In some of them the distance between the nodal QRS and subsequent P wave (R-P interval) is indicated by numbers representing hundredths of a second.

Upright P waves with uneven spacing, varying between 1.12 and 0.86 seconds, occur throughout the record, indicating a *sinus arrhythmia*. Some of the P waves coincide with QRST complexes. When isolated, they reveal slight variations in size, ascribed, in association with the sinus arrhythmia, to a wandering of the pacemaker within the sinus node. When the sinus rate speeds up to over 68 the sinus impulse is conducted to the ventricles with a normal P-R of 0.18 second (cf. first two beats). When the sinus rate slows below 68 the A-V node escapes. Its retrograde impulses are prevented from activating the auricles by the sinus impulses, occurring simultaneously with, or shortly after, the nodal impulse. There is thus intermittent *A-V dissociation* caused by simple A-V interference.

Perpetuation of the A-V dissociation is prevented by penetration of some sinus impulses into the A-V junction up to or beyond the area of the nodal pacemaker. The extent of this penetration depends on the timing of the sinus impulse within the ventricular cycle. When a P wave occurs shortly after a nodal QRS, 0.09 second or less, the impulse is stopped high up in the A-V junction and A-V dissociation continues (sixth and last P of the lower strip). When the P wave occurs 0.24 second (0.20 second in one instance, not shown) or more after a nodal QRS, the impulse passes the A-V junction with some delay and activates the ventricles, causing an early ventricular beat with some aberrant contour, a *ventricular capture* (fifth beat of the upper strip). When a P wave follows a nodal QRS at intervals of 0.13 to 0.18 second, no ventricular response ensues but a nodal escape fails to occur at the expected time (eighth P of the upper and seventh P of the lower strip). Instead, following a pause that exceeds the interval (0.88 second) between the two successive nodal beats, a sinus impulse is conducted through to the ventricles. Obviously, the stopped sinus impulse ahead of it must have penetrated into the A-V junction but failed to traverse it completely; yet on its way towards the ventricles it passed the nodal pacemaker and discharged it prematurely, thus shifting its "time table". The *conduction* of these sinus impulses is *concealed* and becomes manifest by its effect on impulse formation in a subsidiary pacemaker. Sinus impulses occurring 0.12 second after a nodal QRS at one time (fourth P wave in the upper strip) are stopped without concealed conduction, and at another time (third P wave of the lower strip) are stopped after the occurrence of concealed conduction. In the first case A-V dissociation continues, in the other it is interrupted.

This interpretation, fortified by analysis of the entire material, permits conclusions in this instance of incomplete A-V dissociation, with an average sinus rate of 62 and A-V nodal rate of 68 as follows:

(1) The period of complete unresponsiveness of the A-V junctional tissue to auricular impulses (the absolute refractory phase) occupies at least the first 0.09 second of the ventricular cycle, a normal value. (2) A subsequent "phase of concealed conduction", during which the impulse penetrates partway into the junction (far enough to reach a subsidiary pacemaker), occupies a period of 0.08 second (R-P of 0.12 to 0.20 second). (3) Recovery of A-V junctional tissue so that the impulse can pass completely is attained after the first 0.20 second, again a normal value. (4) The transition of absolute refractoriness to the phase of concealed conduction (at R-P of about 0.12 second) is not sharply delineated. In this short transitional period the response of the A-V junction cannot be anticipated and A-V conductivity may be considered to be in a critical state. (5) A-V conductivity is not depressed since the P-R interval of the conducted sinus impulses is normal (0.18 second). The prolonged P-R interval (0.36 second) of the earliest ventricular capture can be ascribed to a physiologic delay of A-V conduction during the relative refractory phase. (6) The disturbance of rhythm is caused by acceleration of the subsidiary pacemaker in the presence of a sinus arrhythmia. The A-V dissociation can be attributed entirely to normal A-V interference and no abnormal depression (block) of the junction has to be postulated.

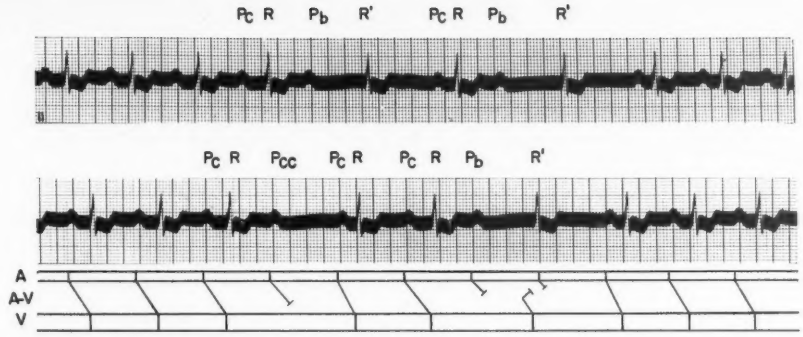

FIG. 3. Concealed A-V conduction preventing nodal escape in second degree A-V block (with two areas of impaired conductivity). The two strips shown are consecutive (but not contiguous) portions of a long lead II. The conventions in the diagram are those used in figures 1 and 2. The symbols P_c, P_{cc}, R and R′ are explained below.

Sinus rhythm is indicated by the regular sequence of upright P waves throughout the record. The ventricular spacing, however, is irregular due to the failure of some sinus impulses (P_b and P_{cc}) to yield a ventricular response. P-R is prolonged in all conducted beats, least (0.22 to 0.24 second) after a ventricular pause, and most (0.32 second) in the last beat of a series ahead of a pause. This is the evidence that a *second degree A-V block (type I)* is responsible for the ventricular pauses. During these pauses the A-V node (R′) escapes, its impulses coinciding with a sinus P wave. Thus, in some instances two P waves in succession fail to activate the ventricles, the first (P_b) due to A-V block, the other (coinciding with R′) due to A-V interference with the escaping nodal impulse.

When the R-R′ intervals of the two nodal escapes in the upper strip are compared, it is found that the second is longer (1.28 seconds) than the first (1.20 seconds). This difference neither precludes the correctness of the interpretation nor does it mean an irregular nodal pacemaker. It can be accounted for if the duration of the A-V conduction time (P_c-R) of the last conducted beat ahead of the escape is taken into consideration. The first P_c-R is 0.08 second longer than the other, exactly by the difference of the R-R′ distance of the two escapes; or, in other words, the distance P_c-R′ is equal (1.56 seconds) in both instances. The explanation is as follows: The delay in A-V conduction time causing prolongation of the first P_c-R takes place, in part, in the A-V junction below the area of origin of the A-V nodal impulse. This delay is more marked at the end of a sequence of conducted beats (as with the first P_c-R) than immediately after a pause (as with the second P_c-R). The longer the delay in this stretch of the A-V junction, the closer the R of the conducted beat comes to the R′ of the escape; but the duration of P_c-R′ will remain the same. The longer R-R′ (1.28 seconds) therefore approaches the actual duration of the nodal interval more closely.

A more complex condition is present in the lower strip. Here, too, two ventricular pauses are caused by intermittent blockage of a P wave; however, nodal escape takes place only during the second pause (containing P_b) with R-R′ measuring 1.24 second and P_c-R′ 1.58 seconds (as in the upper strip). During the longer pause that follows the third beat (and contains P_{cc}) no escape occurs at the anticipated P_c-R′ interval. This failure of the nodal escape to take place when expected is ascribed to partial penetration of the apparently nonconducted sinus impulse (P_{cc}) into the A-V junction discharging the A-V nodal pacemaker ahead of the time of its spontaneous release of an impulse. This partial conduction of the "blocked" sinus impulse is *concealed*, and its presence is revealed only by its effect upon impulse formation in the subsidiary pacemaker. Thus, while the nodal discharge is delayed, the next sinus impulse arrives and finds the A-V junction no longer refractory. Hence, the longest ventricular cycle of the entire record is terminated by a conducted beat and not by an escape.

The interpretation is fortified by comparing, in the entire material, the different response of the A-V junction with the timing of "blocked" impulses (P_b and P_{cc}). Thus, R-P_{cc} measures 0.32 second as compared with R-P_b of 0.30 second; expressed in terms of refractoriness and recovery, with an R-P of 0.30 second the impulse falls into the absolute refractory phase of the A-V junctional tissue and is completely stopped, while 0.02 second later it occurs within the phase of concealed conduction, linking the absolute and relative refractory phases, and penetrates partway into the junction.

In summary, in this complex example of second degree A-V block it can be demonstrated that: (1) Two areas of block are present in the A-V junction, one above, the other below the location of the subsidiary nodal pacemaker; (2) the impulse may be stopped in the upper or lower region of block. Its penetration into the lower region is concealed and revealed by a shift in the timing of the otherwise regular nodal pacemaker; (3) success or failure of an impulse in penetrating to the lower region of block is a function of its timing in the ventricular cycle and depends on the momentary phase of recovery of the A-V junction after the passage of a preceding impulse; and (4) in a record with unquestionable A-V nodal escapes, the beats terminating the longest R-R intervals may be conducted beats and not escapes.

FIG. 4. Concealed A-V conduction in second degree A-V block causing blockage of consecutive sinus impulses and apparent prolongation of nodal escape intervals. The conventions in the diagram are the same as in figure 2; the additional horizontal line dividing the area A-V (representing the A-V junction) indicates the level of the site of the nodal pacemaker. The numbers between horizontal arrows indicate, in hundredths of a second, the distances between P waves and QRS complexes, or between successive QRS complexes, corresponding to the arrow heads at each side. The symbols P_c, P_{cc}, R and R′ are the same as used in figure 3. The four strips are a continuous portion of a long lead II; the last QRS of the first and third strip is reproduced as the first QRS of the second and second QRS of the fourth strip, respectively; the last P wave of the second strip as the first P wave of the third strip.

The presence of *sinus rhythm* is indicated by regular upright P waves at a rate of 65; the presence of a *second degree A-V block* by failure of single, or two successive P waves to yield a ventricular response, and by progressive prolongation of P-R when A-V conduction occurs several times in succession (cf. top strip). The ventricular pauses engendered by the blockage of auricular impulses are terminated by *nodal escapes* interfering with sinus impulses, except in the fourth and last beat of the third strip. These latter two beats are considered to be sinus beats conducted with the shortest P-R intervals (see below).

The distance of the nodal escapes to the last preceding conducted ventricular beat (R-R′) varies; it falls into two categories: (1) shorter ones (1.46 to 1.76 seconds), when the escape occurs after a single blocked P wave and (2) much longer ones (2.50 to 2.70 seconds), when the escape follows two blocked P waves. In both categories the intervals from the escape to the penultimate preceding P wave (P_c-R′ or P_{cc}-R′) are fairly constant as indicated by the horizontal arrows (ranging from 1.86 to 1.96 second). In one instance (the first two beats of the third strip), two escapes occur in succession, revealing the approximate duration (1.88 second) of the escape interval (R′-R′). This interval would be precisely equal to the actual duration of the nodal cycle were the conduction times of the successive nodal impulses to the ventricles equal. Were the conduction time of the first longer than that of the second, then the actual nodal cycle would be a little longer than the manifest R′-R′ interval. Were the conduction time of the second longer than that of the first, then the actual nodal cycle would be a little shorter than R′-R′. The latter seems to be the case here.

Similarly, the differences in the shorter escape intervals (gaged by their P_c-R′ distance) which do not exceed 0.12 second, can be explained by variations of the conduction times below as well as above the nodal pacemaker; in addition, a slight instability of the discharge rate of the nodal pacemaker might be present. However, the several long ventricular pauses during which nodal escape fails to occur at the anticipated time cannot be explained on this basis. They are attributed to the phenomenon of *concealed A-V conduction*. The clue to this interpretation is provided by three facts: (1) the association of these long intervals with two successively blocked P waves; (2) the constancy of the distance between the escapes and the preceding penultimate P wave regardless of whether

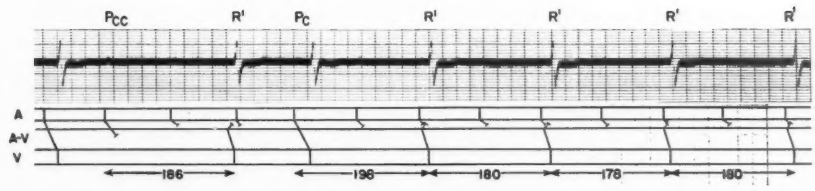

FIG. 5. Concealed A-V conduction in incomplete A-V dissociation due to second degree A-V block causing blockage of two consecutive sinus impulses and postponement of an A-V nodal escape. Another record (lead II) of the case illustrated in figure 4, obtained 10 weeks earlier, with the same conventions used in the diagram.

Small upright P waves (rate 67) indicate a regular sinus rhythm. Only the first and fifth sinus impulses are conducted, yielding the first and third ventricular beat. All other ventricular complexes represent beats of nodal origin, interfering with transmission of independent sinus impulses. The nodal pacemaker (rate 34) has come into operation during ventricular pauses caused by a *second degree A-V block*. On this basis, in the second half of the record, from the fourth to the last ventricular beats, A-V dissociation has developed; one half of the sinus impulses being blocked, the others interfering with impulses of continuous nodal escapes. The nodal interval (1.8 seconds) is twice the sinus interval (0.90 second); hence, in this portion of the record, the position of P within the ventricular cycle is fixed. The unusual feature of the record is the failure of a nodal escape to occur at the expected time during the long pause (2.5 seconds), following the first ventricular beat. Here, two blocked P waves occur in succession and furnish the clue for the delayed appearance of the nodal escape.

The reason for the apparent inconsistency, *concealed A-V conduction*, is indicated in the diagram. The distance between the first of the two consecutively blocked P waves and the QRS complex terminating the long pause (P_{cc}-R′) is similar to that between the conducted beat and the subsequent escape (P_c-R′) and that between two consecutive escapes (R′-R′). This suggests that the second sinus impulse, unlike others in the record, is not blocked high up in the A-V junction but only after penetrating beyond the point of origin of the A-V nodal pacemaker. This penetration causes: (1) disturbance in the regular discharge of the nodal pacemaker and (2) refractoriness in the A-V junction of sufficient degree to cause blockage of the subsequent sinus impulse.

Note that both P_c-R′ (1.98 seconds) and P_{cc}-R′ (1.86 seconds) are longer than R′-R′ (1.80 seconds). This is to be expected since the former two intervals include the conduction times from the auricles to the nodal pacemaker and from the nodal pacemaker to the ventricles in addition to the nodal cycle R′-R′. The fact that P_{cc}-R′ is shorter than P_c-R′ is attributed to the shortening of the conduction time between the nodal pacemaker and ventricles subsequent to the longer period of rest in that area. However, a slight irregularity of the nodal pacemaker must also be present since the difference (0.06 second) between P_{cc}-R′ and R′-R′ is too brief to cover the entire A-V conduction time.

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the latter yields a ventricular response (P_c) or not (P_{cc}); and (3) the occurrence, on occasion, of two nodal escapes in succession, revealing the approximate duration of the simple nodal interval R′-R′, which approaches the duration of the P_c-R′ and P_{cc}-R′ intervals. It thus becomes apparent that the first of two successively blocked sinus impulses penetrates into the A-V junction, beyond the nodal pacemaker, and is blocked somewhere between this pacemaker and the ventricles. In doing so it sets up refractoriness of the A-V junction as if it had traversed the junction completely, and it discharges the A-V nodal pacemaker before it can spontaneously release an impulse and thus shifts the timing of the latter which is expected to occur at intervals of about 1.90 second.

On two occasions (the fourth cycle of the third strip, and the last cycle of the third strip or first cycle of the fourth strip) the long ventricular interval is terminated by a beat which, in view of the whole record, has to be considered a conducted one and not an escape; these beats come too late to represent escapes. Here, too, penetration of and concealed nodal discharge by a preceding sinus impulse took place, permitting termination of a long cycle by a sinus beat (fig. 3).

In this case, therefore, concealed A-V conduction is revealed by both of its usual manifestations; the failure of two successive sinus impulses to reach the ventricles and the failure of a nodal escape to occur at the expected time.

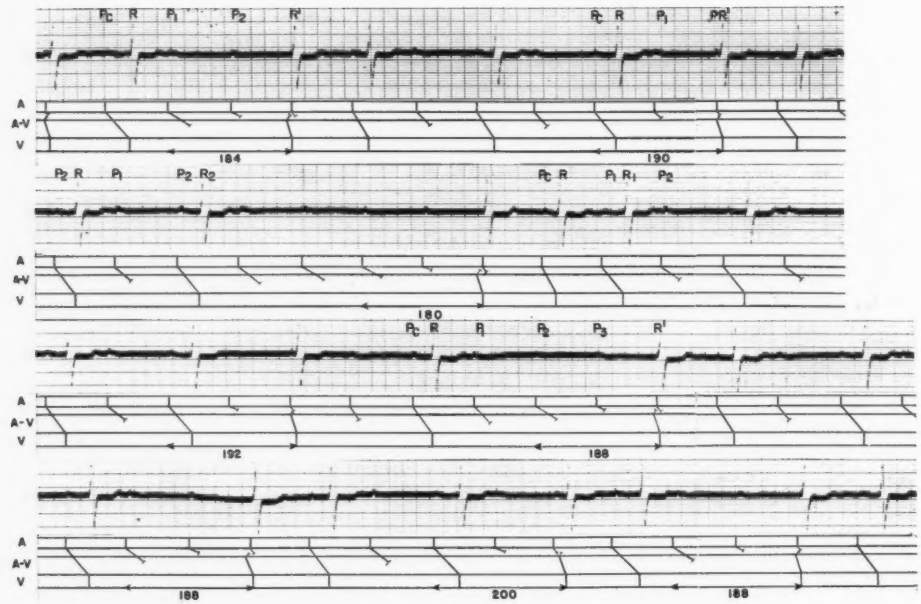

FIG. 6. Second degree A-V block with unusually long ventricular pauses caused by repetitive concealed A-V conduction. The four strips are a continuous record of lead II in the same case as illustrated in figures 4 and 5, obtained one week after record in figure 4. The last P-QRS combination of each strip is reproduced as the first one of the subsequent strip. The conventions in the diagram and symbols are those used in figures 4 and 5.

The auricular rate is regular throughout and corresponds to a sinus rhythm at a rate of 62. The ventricular beating is slower and irregular because: (1) many auricular impulses fail to yield a ventricular response (*second degree A-V block*) and (2) nodal escapes occur at variable R-R′ intervals. The conducted beats have P-R intervals varying between 0.20 and 0.40 second. There is only one instance, towards the end of the second strip, where A-V conduction occurs twice in succession with P-R lengthening from 0.20 to 0.32 second (a frequent occurrence in other portions of the long record not reproduced). Elsewhere, one to four consecutive P waves are blocked following a conducted beat before the A-V node escapes.

There are several unexpected features in this record, apparently inconsistent with the usual events in second degree A-V block. One is the occurrence on some occasions of repetitive blockage of consecutive sinus impulses (with ventricular pauses of 2.44 to 4.24 seconds), whereas consecutive conduction takes place in other instances. Another, is failure on many occasions of P-R to shorten subsequent to pauses engendered by blocked P waves. A third, is the variability of the duration of the ventricular pauses with nodal escapes absent when expected. Implication of the mechanism of *concealed A-V conduction*, as indicated in the diagram, permits a satisfactory interpretation of the record on a uniform basis.

Blockage of impulses penetrating into the A-V junction occurs either above or below the site of the nodal pacemaker. When the impulse is stopped at the upper level, a nodal escape promptly occurs but, unlike figure 4, the actual escape interval cannot be determined since nowhere in the record do two escapes occur in succession. An approximation of this interval, however, is possible by measuring (as in figures 4 and 5) the distance (P_c-R′ and P_{cc}-R′) to the penultimate P wave preceding the escape beats (not counting the P wave which coincides with the nodal QRS). As indicated in the diagram this distance is fairly constant (1.8 to 1.92 seconds, on one occasion 2 seconds), and this is true regardless of whether this impulse yields a ventricular response (P_c) or fails to do so (P_{cc}). It thus becomes apparent that both impulses, P_c and P_{cc} travel to the nodal pacemaker and, by discharging it, set the time for initiation of a new nodal cycle. P_c then penetrates further to acti-

vate the ventricles, while P_{cc} is blocked in the lower levels of the A-V junction, its conduction remaining concealed. P_e-R′ and P_{cc}-R′ represent, therefore, the sum of the unknown nodal escape interval plus the time spent by the sinus impulse P_e or P_{cc} in reaching the nodal pacemaker plus the conduction time of the nodal impulse to the ventricles. The variations in the duration of P_e-R′ and P_{cc}-R′ can be ascribed to variations in the conduction times above and below the nodal pacemaker and/or to a slight irregularity of the nodal discharge. The fact that P_{cc}-R′ (1.80–1.88 seconds) is consistently shorter than P_e-R′ (1.90 to 2 seconds) can mean only that any expected lengthening of the conduction time of impulse P_{cc} above the site of the nodal pacemaker is outbalanced by a shortening of the conduction time of impulse R′ below the nodal pacemaker as a result of the longer rest period in the latter region (fig. 5). Variations in conduction times below the nodal pacemaker appear to be more significant than those above it and this suggests that the subsidiary pacemaker is located in the upper region of the A-V junction as indicated in the diagrams. Variations of the conduction time P_e-R subsequent to an escape (R′) seem to depend on variations of the R′-P_e distance.

Partial penetration of apparently blocked P waves, established in this way, can then be implied to account for the repetitive blockage of P waves as well as for the failure of P-R to shorten when expected. Each such penetration of the impulse sets up varying degrees of refractoriness in the A-V junction so as to lengthen the conduction time to the ventricles of a subsequent impulse, to permit only its partial conduction or to stop its conduction altogether. In the long pauses of the second and third strip, three and two successive sinus impulses, respectively, penetrated to the nodal pacemaker but were blocked below it before reaching the ventricles. Thus, the ventricles remained unstimulated because conduction failed and the spontaneous discharge of the subsidiary pacemaker was shifted several times in succession (*repetitive concealed conduction*).

The conditions determining the great variability of the manifest A-V response can be further unraveled as exemplified diagrammatically in figure 6*A*. In essence, the conduction disturbance present can be viewed as a second degree A-V block, varying between 2:1 and 3:2 ratios, with several intermediate stages resulting from concealed conduction of the 'blocked' auricular impulse. The *extent* to which this impulse (P_1) penetrates into the A-V junction, and whether it is stopped above or below the site of the nodal pacemaker, depends on its R-P distance. The *speed* at which this penetration takes place is determined mainly by the P-R interval of the preceding conducted beat. The interplay of these two factors sets the pattern for subsequent events whether a nodal escape occurs in time, whether its appearance is delayed due to premature discharge by one or several subsequent penetrating impulses, or whether the ventricular pause is terminated by a conducted beat.

The evidence for this interpretation is provided by the following facts: The three P_1 impulses in the record that are blocked high in the A-V junction and do not reach the pacemaker have R-P intervals of 0.56, 0.54 and 0.52 second; all other R-P intervals associated with penetration of impulse P_1 measure 0.54 second or more. Now, one might expect that the blocking effect of the concealed penetration of P_1 upon conduction of impulse P_2 depends on the extent of the penetration of P_1, and, therefore, increases with lengthening of the R-P_1 distance. Yet, paradoxically, so it seems, amongst the P_1 impulses with concealed conduction those with the shorter R-P_1 intervals exert the greater blocking influence upon impulses P_2. Thus, an R-P_1 distance of 0.54 to 0.56 second is associated with blockage of impulse P_2 above the nodal pacemaker; an R-P_1 of 0.56 to 0.62 second with penetration of impulse P_2; and an R-P_1 of 0.60 to 0.68 second with delayed but complete A-V conduction of impulse P_2. The clue to the understanding of this peculiar relationship is found in the varying duration of the conduction time (P_e-R) of the impulse preceding impulse P_1. Since in second degree, A-V block conduction of consecutive impulses is commonly associated with progressive prolongation of the conduction time (until one impulse is blocked), it is reasonable to assume that the time for concealed conduction of impulse P_1 to the site of the nodal pacemaker lengthens when the preceding P_e-R interval is prolonged; and the slower the concealed conduction of P_1, the smaller are the chances for P_2 to enter, penetrate into or traverse the A-V junction. This is in short a *Wenckebach phenomenon of concealed conduction*. Hence, ceteris paribus, it is the speed and not the extent of penetration of impulse P_1 that determines whether impulse P_2 can pass to and beyond the nodal pacemaker or is blocked above it.

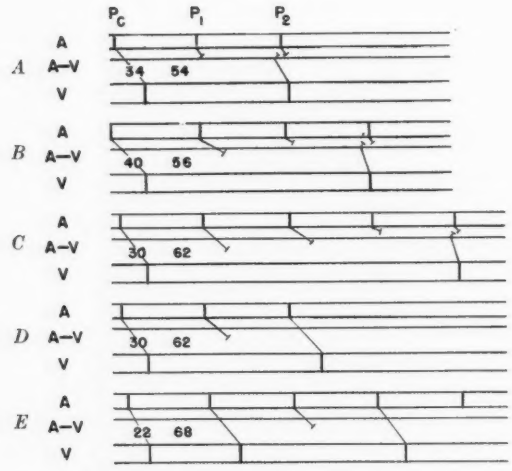

FIG. 6A. A diagrammatic representation of the fundamental conduction disturbance, and its principal variations encountered in figure 6. Intermediate stages between 2:1 and 3:2 A-V block. Extent and speed of concealed conduction. *A* corresponds to a portion of the top strip of figure 6, starting with the tenth P wave; *B* corresponds to another portion of the same strip, starting with the second P wave; *C* represents a portion of the third strip starting with the seventh P wave; *D* starts with the first P wave of the second strip and *E* with the ninth P wave of the second strip. The conventions and symbols are the same as in figure 6. The varying degree of inclination of the oblique lines indicates the varying speed at which sinus impulses traverse or penetrate into the A-V junction. The first number in column A-V (within an oblique line) indicates the length (in hundredths of a second) of the P-R interval of impulse P_c; the number to the right of it the R-P interval of impulse P_1.

The five strips are arranged in such a manner as to demonstrate three intermediate stages (*B–D*) between a 2:1 A-V block with nodal escape (*A*) and a 3:2 A-V block with the Wenckebach phenomenon (*E*). The intermediate stages result from quantitative differences of the effect of concealed conduction of impulse P_1. In *B*, P_1 penetrates slowly to the site of the nodal pacemaker and causes high blockage of the subsequent impulse P_2 so that escape of the node is delayed by about one sinus cycle. In *C*, P_1 penetrates to the same extent but at somewhat faster rate; this in turn permits penetration of impulse P_2 to the nodal pacemaker so that the nodal escape is delayed by about two sinus cycles (*repetitive concealed conduction*). In *D*, nodal escape is delayed by penetration of P_1 but impulse P_2 succeeds in slowly traversing the junction so that the pause is terminated by a conducted beat.

These different effects of impulse P_1 upon subsequent events, evidently dependent upon both the degree and the speed of its penetration, can be further analyzed in the following manner: the *extent* to which P_1 penetrates into the A-V junction is clearly determined by its R-P_1 distance. Thus, in *A*, where R-P measures 0.54 second, P_1 is blocked above the nodal pacemaker. In *B–D*, with R-P_1 distances of 0.56 to 0.62 second, P_1 passes beyond the site of the nodal pacemaker but fails to reach the ventricles. In *E*, with an R-P_1 of 0.68 second, P_1 traverses the junction completely. The *speed* at which P_1 travels through the junction under these various circumstances appears to depend primarily on the preceding P_c-R interval. This is demonstrated by comparison of *B* and *C*. In *B*, where P_c-R is longer (0.4 second) and R-P shorter (0.56 second), P_1 travels slower (and has a more marked effect on P_2) than in *C* where P_c-R is shorter (0.3 second) and R-P_1 is longer (0.62 second). Comparison of *C* and *D*, however, reveals that R-P_1 and P_c-R intervals cannot be the only factors which influence the effects of P_1 upon subsequent impulses. The values are the same in both instances, yet in *C*, P_2 fails to traverse the junction, while in *D*, it succeeds in doing so. Other factors operating during the "critical phase" of A-V conductivity (see text) may be invoked to account for such variations in the expected events.

part of the ventricular cycle to which partial penetration of the A-V junction by sinus impulses seems limited under normal conditions. However, we realize that with this method of determination, one may underestimate the duration of the phase of concealed conduction. It is conceivable that, when gaged by its other effect, viz., upon transmission of the subsequent impulse, concealed conduction may already become manifest when the impulse has not yet penetrated far enough to reach the site of the subsidiary pacemaker.

In cases of sinus rhythm with second degree A-V block, or auricular fibrillation,

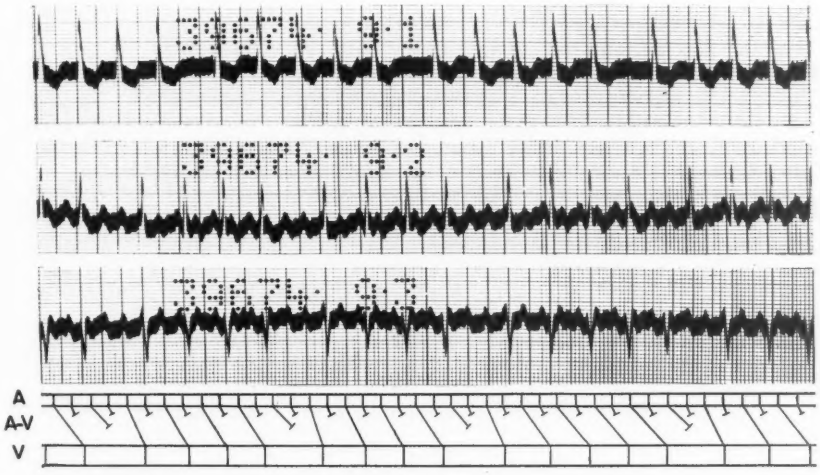

FIG. 7. Blockage of consecutive impulses in auricular flutter, with ventricular group beating due to two regions of impedance to A-V conduction. Conventions in the diagram are the same as in figure 1.

Regular continuous undulations of the baseline (F waves), best seen in leads II and III, indicate the presence of *auricular flutter* (rate 316). The ventricular response is irregular; groups of four or five faster beats are separated by pauses. The R-R of the faster beats is a little longer than two F-F intervals; the R-R of the pauses is shorter than four but longer than three F-F intervals. Within each run of ventricular beats the R-R progressively shortens so that the last R-R before a pause is invariably shorter than the first R-R following a pause. The R-R between the initial beats of two consecutive fast groups is an exact multiple (10 or 12) of the F-F interval. This grouping of the ventricular beating, and recurrence of a characteristic R-R spacing within and between the groups, indicates the operation of the *Wenckebach mechanism* in the transmission of every other flutter impulse to the ventricles.

As indicated in the diagram, alternate flutter impulses are stopped high in the A-V junction so that the *effective* auricular rate, that is the number of impulses penetrating deeper into the junction, is reduced to half the flutter rate. Four out of five, sometimes five out of six, of these effective impulses traverse the junction and activate the ventricles, the last of each such group being blocked. Hence, two areas of impedance to A-V conduction are in operation: One, acting at a higher level, reduces the number of flutter impulses to become effective; this may be considered an area of *physiologic interference* resulting from the normal refractoriness of A-V junctional tissue to rapid stimulation; the other, operating at a lower level, causing Wenckebach periods with dropping out of every fifth or sixth ventricular response to the "effective" flutter impulses; this may be considered a manifestation of *block* caused by an abnormal depression of conductivity in the lower A-V junction.

Although one of the characteristic manifestations of concealed A-V conduction seems to be present, namely, blockage of several auricular impulses in succession with varying penetration of the A-V junction, this mechanism need not be invoked here. With rapid auricular rates, implication of two areas of impedance, as outlined above, may be sufficient to account fully for the failure of several consecutive auricular impulses to traverse the A-V junction.

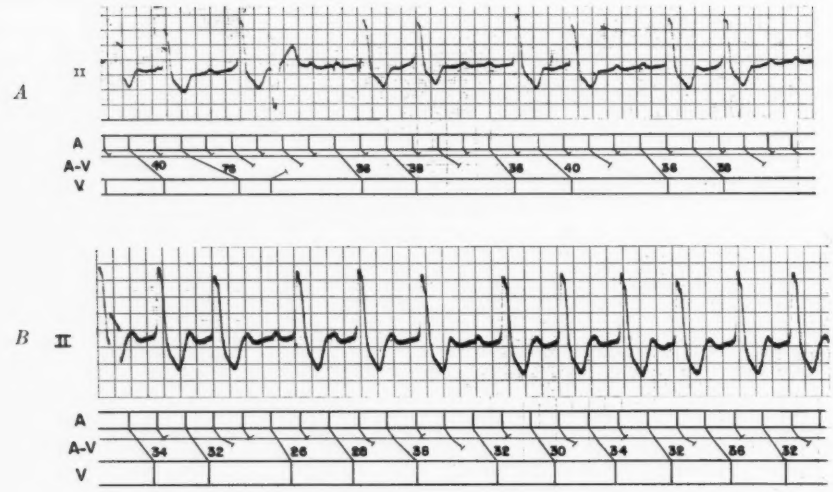

FIG. 8. Auricular tachycardia with ventricular group beating (bigeminy) caused by two regions of A-V block (A), and by concealed A-V conduction (B).

The two records were obtained several days apart; conventions in the diagrams are the same as in figure 1. The additional horizontal line at the level of A-V indicates an area of block in the upper part of the A-V junction. The numbers indicate the duration of the P-R intervals in hundredths of a second.

In *A*, the auricular action is rapid (176) and regular (*auricular tachycardia*), while the ventricular rate is slower and irregular. Throughout the record there is grouping of ventricular beats, in that short cycles alternate with long ones (*bigeminy*). All ventricular complexes except the fourth (*a ventricular premature systole*) are alike and are due to conducted auricular impulses; their QRST contour is abnormal because of intraventricular block. In most of the record the long ventricular cycles are a little shorter than four P-P intervals and the short ventricular cycles a little longer than two P-P intervals; the interval between corresponding beats measures exactly six P-P intervals. In the beginning of the record this consistency in ventricular spacing is disturbed: the second, third and fourth cycles are shorter than corresponding cycles of the ventricular bigeminy seen elsewhere in the strip. However, the interval between the first and fifth ventricular beat is again an exact multiple (10 times) of P-P.

On the basis of these measurements the following interpretation, which is indicated in the diagram, is suggested: A-V conduction of the rapid auricular impulses is impaired by the presence of *two levels of block* in the A-V junction. Only every other auricular impulse traverses the upper and penetrates into the lower level of block. These impulses, while traveling toward the ventricles are either delayed or blocked. Usually, of three successive penetrating impulses the second is more delayed than the first and the third is stopped; this causes the bigeminy present in most of the record with P-R intervals alternating between 0.36 and 0.38 to 0.41 second. On one occasion (first portion of the record) the third successive penetrating impulse manages to reach the ventricles, though with a very long P-R of 0.76 second, and the next (fourth) penetrating impulse would be expected to be blocked (a 3:2 response being changed to a 4:3 response). But at this time a ventricular premature systole occurs which, by retrograde spread of its impulse, prevents transmission of another penetrating auricular impulse and causes a true compensatory pause. Thus, bigeminy is maintained. Similarly, as in figure 7, the two areas of conduction impedance (both caused by depression of the A-V junction) can account for the unusual A-V ratio and there is, therefore, no need to implicate the mechanism of concealed conduction.

In *B*, at a slightly slower (167) auricular rate, ventricular bigeminy, on a different basis, is seen in the second half of the record. Its longer cycles measure a trifle more and its shorter cycle a trifle less than two P-P intervals. The distance between corresponding beats equals exactly the length of four P-P intervals. In the first half of the record the alternation of long and short cycles involves only the first three beats. Subsequently, two longer pauses occur, both shorter than three P-P with two

flutter or tachycardia with a slow ventricular rate, delay or failure of appearance of escape beats can be attributed to concealed A-V conduction and discharge of the subsidiary pacemaker by some of the apparently blocked auricular impulses. Under such circumstances, a subsequent auricular impulse, occurring after recovery of A-V conductivity, may cross the junction to activate the ventricles before a delayed escape takes place (figs. 3 through 6). Thus, in a record with unquestionable A-V nodal escapes, contrary to the rule, the longest ventricular interval may be terminated by a conducted beat and shorter intervals by escapes (fig. 3). On occasion, the distinction between the two types of beats may become difficult or impossible, unless they are characterized by differences in contour.[38, 39]

In figures 3 through 6, a method is demonstrated to determine whether an A-V nodal escape or a conducted beat terminated the pause engendered by concealed conduction with blockage of successive auricular impulses. The interpretation of such cases is greatly simplified by the occurrence in the record of two or more unquestionable escapes in succession (figs. 3, 4 and 5), providing an approximate measure of the actual cycle length (R′-R′) of the subsidiary pacemaker. The interval between a P wave (P_c) of a conducted beat and an escape that follows (P_c-R′) is expected to be longer than the interval between two consecutive escapes (R′-R′), since the former includes the conduction time of the impulse from the sinus node to the site of the subsidiary pacemaker plus the conduction time from the subsidiary pacemaker to the ventricles. This is equally true if a sinus impulse (P_{cc}) traverses the A-V junction but is stopped in its path to the ventricles after it has reached and discharged the subsidiary pacemaker; hence, the distance between P of the conducted or partially conducted impulse and the escape (P_c-R′ and P_{cc}-R′) will tend to

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shorter cycles in between. Again the comparison of ventricular with auricular cycles suggests that the grouping of ventricular beats is caused by a complex conduction disturbance in the A-V junction as indicated in the diagram.

Fundamentally, a 2:1 conduction ratio is present with varying penetration of the A-V junction by the "blocked" auricular impulses. Ventricular bigeminy is the result of alternation of shorter and longer P-R intervals of the conducted impulses, which is caused by deeper penetration of alternate "blocked" impulses. Little or no penetration permits the subsequent P-R to shorten; this in turn enhances penetration of the following blocked impulse; the more extensive penetration of this lengthens the subsequent P-R and consequently penetration of the following blocked impulse is again reduced; thus the sequence starts anew. During the irregularity with the two longer pauses seen in the first part of the record, a second factor seems in action in addition to varying penetration of blocked impulses, namely, the influence of cycle length upon the refractory period. The details are as follows: the first two ventricular beats show alternation of P-R as seen during the bigeminy at the end of the strip. However, subsequent to the shorter (0.32 second) of the two P-R intervals, two auricular impulses are blocked in succession. Apparently here, for reasons unknown, the first of the two penetrated deeper than usual causing more refractoriness of the A-V junction and thus transiently changed the fundamental 2:1 A-V ratio to a 3:1 ratio—actually an attempt at 3:2 conduction (fig. 1). The result is the first longer ventricular pause which in turn has the following effects: it permits subsequent shortening of P-R to 0.26 second and thus lengthens the R-P of the next auricular impulse; on the other hand, it prolongs the refractory phase so that penetration of the blocked auricular impulse after this short P-R interval becomes minimal. Consequently, the P-R remains also short (0.28 second) in the next conducted beat. Only after this beat does deeper penetration of the blocked auricular impulse take place and, in turn, causes lengthening of the subsequent P-R to 0.38 second. The following pause, too, is caused by a transient change of a 2:1 to a 3:1 A-V response, but here it is due to the failure of an impulse to traverse the junction because of shortening of its R-P distance. As a consequence, the subsequent auricular impulse succeeds in doing so, though at a longer P-R (0.32 second) and this initiates the bigeminy analyzed above.

In this record, in contrast to record A, the ventricular bigeminy cannot be explained merely on the basis of two levels of block in the A-V junction. Here, concealed A-V conduction must be postulated. The two mechanisms are not exclusive and may operate in the same case on different occasions or simultaneously in conjunction (fig. 3).

be equal. Slight differences can be expected and explained by variations in the A-V conduction times above and below the subsidiary pacemaker, and/or some irregularity in the discharge of the latter.[21] Whenever distances between P of a conducted impulse (P_c) and R of a subsequent beat are found considerably longer than the established P_c-R′ distance, in other words, whenever the escape fails to appear at the expected time, concealed conduction of the subsequent interposed and apparently blocked P wave has to be postulated (figs. 3, 4 and 5). As stated before, under such circumstances the auricular impulse that follows the concealed discharge may be conducted to the ventricles before the delayed escape is due, so that the long R-R interval is terminated by a conducted beat and not by an escape. Thus, if the distance between P_{cc} (the "blocked" P following P_c) and the subsequent R approaches the established P_c-R′ distance, R represents an escape; if it is considerably shorter, the beat terminating the pause engendered by concealed conduction is identified as a conducted beat (figs. 3 and 4). This method can also be applied when blockage involves more than two sinus impulses in succession (fig. 6), by measuring the distance from each of the consecutively "blocked" P waves, to the next R wave and comparing it with an established (P_c-R′) or (P_{cc}-R′) distance. Under such circumstances, partway penetration of impulses into the A-V junction may be responsible for both repetitive extraneous discharge of a subsidiary pacemaker, "ahead of schedule," and repetitive blockage of consecutive impulses above or below the site of this pacemaker. As indicated in two instances of figure 6, such a mechanism may result in prolonged ventricular asystole with apparent failure of the subsidiary pacemaker to take over.

The record illustrated in figure 6 is of particular interest because, in spite of the great variations in manifest A-V response (varying between 3:2 and 5:1), the disturbance can be shown to represent essentially an A-V block varying between 2:1 and 3:2 with tendency to concealed conduction of the "blocked" impulse. This is demonstrated in figure 6A. Depending on both the *extent and speed of concealed conduction*, three intermediate stages between the ratios of 2:1 and 3:2 A-V response can be defined and actually identified in the record. The auricular impulse that follows the partially conducted one may: (1) be blocked above the site of the subsidiary pacemaker, (2) penetrate beyond the subsidiary pacemaker but fail to reach the ventricles (*repetitive concealed conduction*), or (3) yield a ventricular response after a delay. Evidently, with repetition of concealed conduction, further patterns of A-V response may develop in that repetitive concealed conduction may again be responsible for the same threefold effect upon conduction of the subsequent impulse and discharge of the subsidiary pacemaker.

Failure of several consecutive auricular impulses to cross the A-V junction, one of the principal manifestations of concealed AV-conduction, is encountered commonly in auricular flutter and auricular tachycardia upon exhibition of digitalis. Here, however, the mechanism usually is different and, in the presence of even conduction ratios (for example, 4:1) or group beating of the ventricles, can be explained without implication of concealed conduction. Since the normal refractory phase of the A-V junction is longer than that of the auricles, its reaction to rapid stimulation (that is, at rates over 200) is a 2:1 response which reduces to one half the number of impulses penetrating into the junction. This is a normal protective mechanism of the heart, preventing rapid ventricular rates. On the other hand, digitalis primarily depresses A-V conduction of the "effective" impulses as they spread toward the ventricles. Thus, two areas of impedance to A-V transmission of impulses are created: one, high up in the junction, caused by physiologic interference, the other, at a lower level, caused by abnormal depression with block; the former, with a regular 2:1 response, the latter, showing all varieties of second degree A-V block. Irregularity of ventricular beating or grouping of ventricular beats (for example bigeminy) can, in the majority of cases, be unraveled by identifying the structure of simple Wencke-

bach periods in the ventricular response to the effective impulses occurring at half the actual auricular rate[26] (fig. 7).

Concealed A-V conduction may, of course, also occur with rapid auricular rates or complicate the mechanism of the double area of conduction impedance. Thus, varying penetration of the region of interference by the "ineffective" auricular impulses has to be implicated to account for alternation of ventricular cycle length in cases of auricular flutter with a persistent 2:1 ventricular response.[10, 15, 22] More pronounced penetration of every second impulse, representing attempts at 3:2 A-V conduction may result in the uncommon occurrence of a 3:1 conduction ratio in auricular flutter. In auricular tachycardia with less rapid rates (below 200), irregular ventricular response and failure of several successive impulses to traverse the A-V junction can be explained on a similar basis as in auricular flutter; one merely has to postulate two levels of depressed conductivity instead of the combination of one of physiologic interference with one of abnormal block (fig. 8).

Varying penetration of auricular impulses altering refractoriness of the A-V junction to subsequent impulses occurring in rapid succession can, at least in part, account for the complete irregularity of the ventricular action in auricular fibrillation.[27, 28]

While the phenomenon of concealed conduction is most readily and most commonly demonstrable in the A-V junction, it can be invoked to account for certain features of impaired intraventricular conduction as well. The supraventricular impulse that reaches the site of a blocked bundle branch via the septum, may affect the recovery time of the defective bundle branch system and thus influence propagation of the subsequent supraventricular impulse. Two well known phenomena find their explanation in such *concealed intraventricular conduction*: (1) the rare manifestation of second degree block of intraventricular conduction,[40] and (2) the perpetuation of aberrant ventricular conduction, initiated by the resumption of a rapid ventricular rate subsequent to sudden transient ventricular slowing; this occurs in auricular tachycardia with second degree A-V block,[41] or, more commonly, in auricular fibrillation with rapid ventricular rate.[42, 24] A somewhat similar mechanism, concealed retrograde intraventricular conduction, can be postulated in cases of pre-excitation with auricular fibrillation[43, 44] to account for the peculiar grouping of beats with normal and anomalous conduction, with transitional complexes in between. It would appear that in these cases an impulse, conducted over one of the two available conduction pathways tends to enter the other in a retrograde fashion, to render it refractory for the subsequent supraventricular impulse. Finally, the occurrence of concealed conduction of the impulse within a re-entry path was postulated in certain cases of intermittent bigeminy, due to ventricular premature systoles. Such an incomplete penetration of the re-entry path may become manifest in an unexpected prolongation of the coupling of a subsequent premature systole,[45] or the failure of the premature systole to occur when expected.[37] A similar mechanism was proposed by Schott[46] to account for inconsistencies in the occurrence of parasystolic beats.

The short period of concealed conduction during which an impulse penetrated partway into the preformed conduction pathways, ordinarily is sandwiched between the period of absolute refractoriness, causing complete failure of conduction and relative refractoriness, permitting passage of impulses at slow speeds. Clinical records with disturbances of cardiac rhythm can be found in which, as in the controlled animal experiment, the time span within the cycle during which only concealed conduction takes place, can be separated from the periods of absolute and relative refractoriness and expressed in terms of R-P intervals (fig. 2). The demarcation may be sharp or there may be some overlap in either direction. In dealing with cases with depressed A-V conductivity this overlap is usually more marked; in fact, the phase of concealed conduction may become inseparable from the end of the absolute and the beginning of the relative refractoriness, so that within a certain

range of R-P intervals the response of the A-V junction is unpredictable. Thus, a "critical period"[28] may be present during which, at the same R-P interval, the impulse sometimes is blocked, sometimes may pass at a long P-R interval, and sometimes penetrates into the A-V junction without reaching the ventricles.

There are several factors which might influence the extent of passage of an impulse occurring in such a critical phase of conductivity. It may be extraneous influences, in particular, momentary alterations of vagal tone; or it may be the effect of the duration of the preceding cycle, shortening or lengthening refractoriness of the A-V junction (fig. 8*B*). These two factors may operate with normal as well as depressed conductivity. When conductivity is depressed, a third factor, namely, a supernormal phase of recovery, may come into play to influence the response of the A-V junction to individual impulses.

A supernormal phase of conduction may be responsible for the occurrence of concealed conduction, in that an impulse that otherwise would be blocked may penetrate into the conducting tissues. The phases of concealed conduction and of supernormal conduction can be expected to overlap in various ways, rather than show a fixed temporal relationship, and the manifestations of the supernormal phase can be expected to vary accordingly. Thus, as a result of supernormal conduction, the phase of concealed conduction may be shifted to the left of the recovery curve and widened, abbreviating the absolute refractory phase. If supernormal conductivity affects only the last portion of the phase of concealed conduction, the expected result is a shortening of the phase of concealed conduction and a lengthening of the relative refractory period. On the other hand, there may be no change in the location or duration of the phase of concealed conduction, but, impulses occurring during its earlier portion may penetrate at a faster speed and have a less marked effect on the conduction of subsequent impulses than those occurring during its later portion; for the same reason impulses which occur during the early portion of the phase of concealed conduction may reach and discharge another pacemaker, whereas those occurring later may fail to do so. Evidently, if the supernormal phase of conduction permits not only partial penetration but full conduction of early impulses, and if the phase of concealed conduction outlasts the phase of supernormal conduction, a period of full conduction may precede a period of concealed conduction. In short, the supernormal phase of conduction may manifest itself merely in a change of the duration of the phase of concealed conduction: lengthening it by shortening the absolute refractory period, or shortening it by lengthening the relative refractory period. Under such circumstances the presence of a supernormal phase of conduction may easily remain unrecognized. By contrast, it will become manifest by the occurrence of: (1) more rapid conduction of the earlier fully conducted impulses compared with later ones, (2) full conduction of earlier impulses and only partial (concealed) conduction or nonconduction of later impulses, or (3) deeper or faster penetration of the earlier impulses amongst those which are only partially conducted.

Concealed conduction of impulses is not restricted to forward conduction through the A-V junction, but may affect retrograde spread of impulses as well. The simplest and most common result of concealed A-V conduction in retrograde direction, the compensatory pause or the P-R lengthening after interpolated premature ectopic beats, has been mentioned. Less frequent and more involved manifestations are the occurrence of double blockage of retrograde A-V nodal impulses in A-V nodal tachycardia[24, 28] and the occurrence of concealed re-entry of the nodal impulse in reciprocal beating.[20] On the other hand, concealed retrograde conduction of A-V nodal impulses may also be responsible for a state of supernormality influencing forward conduction of subsequent sinus impulses.[28, 47] An analogous mechanism was postulated for retrograde conduction of ventricular or A-V nodal impulses after concealed conduction of sinus impulses.[48] Under such circumstances an extraordinary condition may result in which concealed conduction may enhance rather than inhibit the conduction of a subsequent impulse.

Conclusions

1. Conductivity of the A-V junction cannot be gaged by the ratio of the manifest A-V response.

2. When two consecutive auricular impulses fail to traverse the A-V junction the mechanism of concealed A-V conduction has to be considered. Apparent 3:1 A-V conduction may actually represent an abortive attempt at 3:2 A-V conduction.

3. Intermediate stages between 2:1 and 3:2 A-V response can be defined, depending upon the quantitative effect of concealed conduction of the "blocked" impulse. Concealed conduction may cause delayed transmission, partial penetration (repetitive concealed conduction) or complete blockage of the subsequent impulse.

4. The effects of concealed conduction depend not only on the extent, but also on the speed of penetration of the "blocked" impulse. Regardless of the ultimate extent of penetration, the slower the speed of concealed conduction, the more marked is the effect upon conduction of the subsequent impulse.

5. In repetitive concealed conduction involving more than two consecutive impulses, a Wenckebach phenomenon of concealed conduction can be postulated.

6. Occurrence of concealed A-V conduction in incomplete A-V dissociation, revealed by occasional concealed discharge of the A-V nodal pacemaker, permits approximate determination of the duration of the phase of concealed A-V conduction.

7. In second degree A-V block, occasional concealed discharge of the subsidiary A-V nodal pacemaker by a penetrating ("blocked") auricular impulse may cause the longest ventricular intervals to be terminated by conducted beats and shorter ones by escapes.

8. Repetitive concealed conduction, responsible for repetitive concealed discharge of the subsidiary pacemaker, may account for prolonged ventricular asystole.

9. In the presence of rapid auricular rhythms, the mechanism of a double region of impedance to A-V conduction or the mechanism of concealed A-V conduction may be responsible for group beating of the ventricles. The two phenomena are not mutually exclusive.

10. Concealed conduction may give rise to hitherto undescribed manifestations of the supernormal phase.

11. When A-V conductivity is depressed, an overlap of the phase of concealed conduction with the absolute and/or relative refractory phase may result in a "critical period" of the cycle, during which the response of the A-V junction cannot be predicted.

12. Recognition of concealed conduction is indispensable for the understanding of disturbances of conduction and formation of the cardiac impulse.

Summary

1. Concealed conduction, a neglected but important phenomenon of impaired conductivity, occurring under physiologic and pathologic circumstances, consists of incomplete penetration of preformed conduction pathways by an apparently blocked impulse. It manifests itself by its effect upon conduction or formation of a subsequent forward or retrograde impulse.

2. Nine selected clinical records with various types of conduction disturbance are presented, illustrating the application of the concept of concealed conduction to the analysis of simple and complex arrhythmias, and demonstrating the usefulness of the concept in the understanding of otherwise unexplainable features.

3. The most common example of concealed A-V conduction affecting *transmission* of a subsequent impulse is the compensatory pause after ventricular premature systoles and the P-R prolongation subsequent to their interpolation. Concealed conduction is responsible for double or multiple blockage of consecutive auricular impulses occurring at slow, normal or moderately rapid rates. When the auricular rate becomes faster than 200, as in auricular flutter, failure of the A-V junction to respond to consecutive impulses can be explained by a different mechanism, namely, two areas of conduction impedance, one due to physiologic interference, the other due to abnormal block. However, concealed A-V conduction may complicate the latter

mechanism; thus, the two mechanisms may operate in the same case on different occasions or in conjunction.

4. The effect of concealed conduction upon *formation* of impulses becomes manifest by altering the expected appearance time of impulses of a subsidiary pacemaker. Thus, in A-V dissociation, the regular cycle of a nodal pacemaker may be periodically disturbed by unsuccessful attempts of sinus impulses at capturing the ventricles. Or, in second degree A-V block, nodal escapes may fail to occur when expected. When such a concealed nodal discharge occurs several times in succession, long ventricular pauses may ensue and it may be difficult to determine the origin of the beat terminating such pauses, whether ectopic or conducted. A method is demonstrated which permits such a differentiation.

5. The phase of concealed A-V conduction, that is the short period of the cycle between the absolute and relative refractory phases, during which impulses penetrate into the A-V junction without traversing it, can sometimes be sharply delineated in terms of R-P intervals. On occasion, however, particularly with depressed conductivity, there may be a considerable overlap with the absolute and relative refractory phase, and their transition may become a "critical period." For such overlaps the operation of a supernormal phase of A-V conduction may be invoked.

6. Principles developed in studying concealed conduction in A-V junctional tissues can readily be applied to account for certain phenomena associated with impaired intraventricular conduction. Thus, concealed intraventricular conduction may account for the rarity of second degree bundle branch block, for continuation of aberrant ventricular conduction in supraventricular tachycardia, for the pattern of impulse spread in certain cases of ventricular pre-excitation, and for variations in appearance and coupling of ventricular premature systoles.

Summario in Interlingua

Es demonstrate que le recognition de celate conduction del impulso cardiac es indispensabile pro le comprehension de multe arrhythmias cardiac. Post un revista historic del concepto de celate conduction, es presentate registrationes pro demonstrar establite e etiam non previemente describite aspectos de celate conduction atrio-ventricular. Postea le manifestationes de celate conduction intraventricular es signalate. Finalmente le relation del phase de conduction celate con le phase supernormal es discutite.

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An Evaluation of a New Anticoagulant, Acenocoumarin (Sintrom)

By MURRAY WEINER, M.D., MARIANO JIMINEZ, M.D., AND IRWIN KATZKA, M.D.

A new coumarin anticoagulant, acenocoumarin (Sintrom) is compared with other hypoprothrombinemic agents in the same human subjects. Comparing doses which result in the same peak prothrombin time, both speed of onset and duration of effect are found to be a function of the rate of biotransformation. Rapid biotransformation results in fast onset and short duration of action and vice versa. Sintrom is intermediate between the slow, long-acting compounds (Dicumarol, Warfarin, Coumopyrin) and the fast, short-acting Tromexan. One 16 to 32 mg. dose of Sintrom rapidly results in a desirable hypoprothrombinemia which is maintained by a single daily dose of 2 to 10 mg.

SINCE the introduction of Dicumarol about 15 years ago, more than a half dozen additional hypoprothrombinemic agents have become available. Because of wide species differences, comparative pharmacologic studies in animals have been of little value in determining the relative merits of these compounds in man. Empirical clinical comparisons of all these compounds in large numbers of patients by any one group of investigators is an almost impossible task. On the other hand, studies of the comparative human pharmacology of these compounds in the same group of individuals represents a rational method for evaluating their properties and hence their probable advantages and disadvantages. This paper describes the application of this concept to a new coumarin compound, acinocoumarin (Sintrom) (G 23350).*

All known coumarin and indanedione anticoagulants apparently have the same fundamental mechanism of action, i.e., an inhibition or alteration in the synthesis of a portion of the prothrombin complex. The differences in activity of these compounds are related primarily to (1) rate and completeness of absorption; (2) rate of metabolism and/or excretion and (3) potency (i.e., amount of drug necessary to achieve a given response). These factors can best be studied by determining the fate of each compound by chemical methods, and correlating this with the prothrombin response. Such studies have previously been carried out in man with four compounds: bishydroxy-coumarin (Dicumarol),[1] ethyl biscoumacetate (Tromexan),[2] phenindione (Danilone) (Hedulin),[3] and 3-(alpha-acetonylbenzyl) 4-hydroxy coumarin (Warfarin).[4] These studies have resulted in the following:

1. No compound induces a detectable prothrombin change in less than 6 to 12 hours even when given intravenously in large doses. So-called therapeutic prothrombin levels are rarely achieved in less than 18 to 24 hours.

2. The duration of prothrombin response is directly related to the persistence of the drug in plasma, i.e., following a single intravenous dose, the more rapidly the drug disappears from plasma, the shorter will be the duration of the prothrombin response (table 1). There is considerable variation in the rate of disappearance of the same drug in different subjects[1-3] and these differences are reflected in the duration of prothrombin response.

3. There are wide individual variations in the *sensitivity* of prothrombin response to a given drug plasma level, i.e., the same drug level in different subjects may result in quite different prothrombin time peaks.[1, 2, 4]

4. Hypoprothrombinemic agents with relatively short duration of action tend to produce a more rapid initial prothrombin response. Conversely, drugs with prolonged duration of

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* Sintrom was kindly supplied to us by Dr. Albert Hemming of Geigy Pharmaceuticals, Division of Geigy Chemical Corp., New York, N. Y.

TABLE 1.—*Duration of Prothrombin Response After Single Doses of Various Agents in Man*

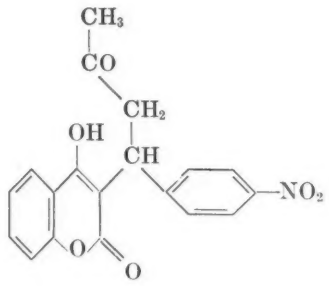
(Doses compared are those which give the same maximum prothrombin time, viz. 23 sec. in whole plasma (control, 13.5 sec.))

Drug	Dose (mg.)	Day of Prothrombin		Half-life in Man (hrs.)	Reference
		Peak	Recovery		
Tromexan	1650	1	2	2.5	2
Sintrom	20	1–2	3		
Phenylindanedione	350	2	4	6.5	3
Dicumarol	400	2–3	5	32.0	1
Cumopyran (63)	150	2–3	5–6		
Warfarin (42)	65	2–3	5–6	90.0	4
Marcumar	24	2–3	6		
Dipaxin	20	3–4	7		

action have a slower onset of hypoprothrombinemia. The speed with which a given prothrombin response is achieved also varies greatly with the dose given.[4] Slow, long-acting hypoprothrombinemic agents can be given in large enough doses to induce a relatively rapid onset of response. However, such large doses may subsequently cause excessive prothrombin deficiency. Comparisons of different drugs regarding speed of onset of effect therefore require that a method be devised for determining which dose of Drug A should properly be compared with a given dose of Drug B. As a rule, the more rapidly the drug is eliminated, the more safely can a rapid onset of effect be induced.

The determination of coumarin or indanedione drug levels by methods previously reported[1-4] requires that the drug be present in plasma in amounts greater than 5 mg. per liter if the rate of disappearance is to be determined. The potency of Sintrom precludes its administration in man in sufficiently large doses to permit significant measurements by these technics. Consequently, prothrombin response is the only basis available in man at present for comparing this drug with other hypoprothrombinemic agents.

Sintrom (acenocoumarin, G-23350), synthesized by Stoll and Litvan,[8] is a coumarin compound with the following structural formula:



Pharmacologic studies by Pulver[5] have demonstrated its anticoagulant properties and several clinical reports have appeared in Europe.[6]

EXPERIMENTAL STUDIES

Single Doses

In order to compare the speed of onset and duration of effect of various hypoprothrombinemic agents in man, it is necessary to determine what single dose of each compound, tested in the same subject, would give the same peak prothrombin response. In our studies, a prothrombin time of 23 seconds* (equivalent to 50 seconds in 12.5 per cent saline-diluted plasma) was chosen as the peak prothrombin effect to be sought in each subject with single doses of each drug. The prothrombin response to various single doses of eight different hypoprothrombinemic agents was studied in each of five subjects. In each instance, at least one week was allowed to elapse between recovery from the previous dose and administration of the next dose. The dose necessary to achieve a peak prothrombin response of 23 seconds (control 13.5 seconds) was thus determined for each drug in each subject. The average dose necessary for this response and the average pattern of the response are summarized in table 1 and figure 1. The half-life of each drug in plasma, as determined by chemical methods applicable to studies in man, is also given in table 1. In this table, the drugs were arranged

* The thromboplastin used was Simplastin,[7] kindly supplied by Dr. George Phillips of the Chilcott Laboratories. The normal prothrombin time with this preparation was 13.5 seconds.

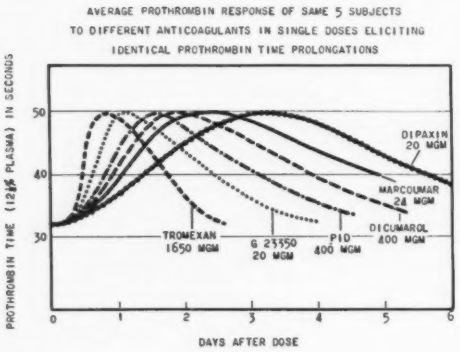


FIG. 1

according to speed of prothrombin response. This same arrangement also holds for speed of recovery of normal prothrombin activity. Neither speed of response nor of recovery correlated with "potency" (with milligrams of drug required to achieve a given peak prothrombin response). The rate of drug metabolism in man as previously determined by chemical methods[1-4] for four of these drugs does correlate with speed of prothrombin response and recovery.

The data indicate that Sintrom, like phenylindanedione, is slower acting than Tromexan, but distinctly faster acting than Dicumarol. Its potency is considerably greater than that of Tromexan, phenylindanedione or Dicumarol.

Multiple Doses

Fifteen patients were treated with Sintrom for a total of 444 patient-days, controlled by 280 prothrombin time determinations. Of these prothrombin determinations (exclusive of the first day of treatment) 39 were below 20 seconds, and 7 were above 40 seconds. Maintenance dosage varied from 2 to 10 mg. per day following an initial dose of 16 to 32 mg. The prothrombin time was above 20 seconds in 10 of the 15 patients 24 hours after the initial dose. Prothrombin time returned to normal within one to two days of the last dose in 14 of the 15 patients treated.

Gross hematuria developed in one subject at a prothrombin time of 48 seconds. Hematuria disappeared within 24 hours of discontinuing dosage. No vitamin K was given. There were no other instances of hemorrhage. In one patient who was very sensitive to the drug, rapid fluctuations in prothrombin response were noted, making control difficult. All others were readily maintained in the desired range of prothrombin activity by daily doses of from 2 to 10 mg. There was no instance of "resistance" to Sintrom.

Three patients have been maintained for alternating periods on Sintrom and phenylindanedione. The ratio of the daily doses of each drug which maintained the same prothrombin time was the same in all 3 patients, i.e., 4 mg. of Sintrom were approximately equivalent to 100 mg. of phenylindanedione.

DISCUSSION

If one considers the previously established relationships of drug plasma level to prothrombin response to other drugs, one might infer the probable metabolic rate of Sintrom by comparing its prothrombin pattern with that of other drugs (fig. 1). These data indicate that Sintrom acts at a rate very similar to that of phenylindanedione, i.e., distinctly more rapid than Dicumarol, but somewhat slower than Tromexan. One might, therefore, predict that with proper initial dosage, "therapeutic" prothrombin levels usually will be achieved within 24 hours, with little danger of a subsequent excessive rise. Repeated daily doses will then be necessary to maintain effect. Discontinuing therapy will result in a prompt return of prothrombin time to near normal in one to two days. These deductions are borne out by the brief clinical experience here presented.

SUMMARY

1. Sintrom, a new coumarin anticoagulant, has been compared with other oral anticoagulants in single doses in the same individuals. It is more rapidly acting than Dicumarol and somewhat slower than Tromexan. In this respect, it closely resembles phenylindanedione.

2. Clinical experience with 444 patient-days of treatment in 15 subjects indicates that a desired degree of hypoprothrombinemia can be rapidly obtained and effectively maintained with this compound. In only one individual were prothrombin time fluctuations so rapid as to make control difficult.

3. No toxic manifestations were noted ex-

cept for one instance of hematuria which was controlled by discontinuing therapy.

4. The properties of Sintrom permit a relatively rapid onset and recovery of hypoprothrombinemia with less likelihood of the very rapid fluctuations of prothrombin time which sometimes results from more rapidly metabolized drugs. In this sense, it strikes a balance between slow, long-acting compounds (Dicumarol, Marcoumar, Warfarin, Coumopyrin) and the very fast, short-acting compound, Tromexan.

5. In terms of milligrams, Sintrom is 25 times as potent as phenylindanedione.

Summario in Interlingua

1. Sintrom, un nove anticoagulante coumarinic, esseva comparate con altere anticoagulantes oral, administrate in doses unic al mesme individuo. Illo age plus rapidemente que Dicumarol e alique plus lentemente que Tromexan. In iste respecto illo es similissime a phenylindanediona.

2. Experientias clinic con un summa total de 444 dies de tractamento in 15 individuos indica que un desirate grado de hypoprothrombinemia es rapidemente obtenibile e efficacemente mantenibile per medio de iste composito. In solmente un individuo esseva le fluctuationes del tempore prothrombinic si rapide que le regulation deveniva difficile.

3. Nulle manifestationes toxic esseva notate, excepte un caso de hematuria que esseva regulate per discontinuar le therapia.

4. Le qualitates de Sintrom permitte un relativemente rapide initiation e recovrantia de hypoprothrombinemia, lo que reduce le risco del rapidissime fluctuationes del tempore prothrombinic que resulta a vices del uso de drogas que es plus rapidemente metabolisate. In iste respecto, Sintrom tene le balancia inter le lente compositos a action prolongate (Dicumarol, Marcoumar, Warfarina, Coumopyrina) e le rapidissime composito a action de breve durantia, Tromexan.

5. Exprimite in milligrammas, Sintrom es 25 vices plus potente que phenylindanediona.

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Relationship of the Natural Body Damping and Body Frequency to the Ballistocardiogram

By Oscar Tannenbaum, M.D., Harry Vesell, M.D., and Jerome A. Schack, M.D.

By means of a direct body ballistocardiograph the relationship of body frequency and damping to the ballistocardiogram in normal subjects was investigated. The influence of age and body measurements were studied and the findings subjected to statistical analysis. The degree of body damping was related to age but not to anthropometric measurements. Overweight and underweight influenced body frequency but not body damping. Respiratory changes had no influence on either body frequency or damping. It was suggested that to record a true ballistocardiogram of the cardiovascular forces more consideration must be given to body damping.

BALLISTOCARDIOGRAPHY is of current interest as a means of studying the forces generated by the heart and great vessels. This discipline is concerned with the resultant of these forces as impressed upon the body, an elastic system forced into vibration and subject to viscous damping.

Many investigators have shown that the vast majority of healthy individuals under the age of 40 have a "normal" ballistocardiogram.[1-4] However, healthy older individuals, with apparently normal cardiovascular systems have a substantial number of "abnormal" ballistocardiograms. It is true that arteriosclerotic heart disease is more prevalent in the older individual, and though "subclinical," may play a part in the deterioration of the ballistocardiogram. However, is this high incidence of "abnormal" ballistocardiograms in the older age group entirely due to latent or incipient coronary artery disease as proposed by some authors?[5, 6]

Changes in the elasticity of the total body mass itself may play an important role in the production of these "abnormal" ballistocardiographic contours. Recent studies have shown that abnormal curves may be made normal by simply changing the damping of the recording system. Thus, Tucker and Ostrom[7] have changed abnormal curves to normal by having the subject lie in a bed of sand or putty or by the use of sandbags applied to the feet and shoulders. Nickerson,[8] by means of a low frequency critically damped system, has obtained tracings which were quite different from those obtained by the use of the high frequency bed of Starr.[9] Attempts have been made to inscribe the ballistocardiogram with elimination of the inherent vibration of the body, by Burger,[10] Von Wittern[11] and Talbot and associates.[12] These investigators have all sought to achieve an essentially aperiodic system.

Much of the investigative work in ballistocardiography has concerned itself with the forces developed by the circulatory apparatus as impressed upon the body mass. Little attention has been directed to the vibratory characteristics of the body itself. Inasmuch as the characteristics of the body as a mechanical oscillator are of considerable importance in the resultant ballistocardiogram, a systematic investigation of the vibromechanical properties of the total body mass was undertaken.

Material and Methods

One hundred normal subjects were selected, ranging in age from 15 to 76 years; 63 males and 37 females. Normality of the cardiovascular system was based on the usual clinical examination, 12-lead electrocardiogram, teleoroentgenogram, urinalysis and hemogram. In the older age group, there were a few individuals with evidence of slight tortuosity of the thoracic aorta on fluoroscopic examination. No attempt was made to secure a basal state. All tracings were recorded with the patient in the re-

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cumbent position on a flat hard wooden surface and during normal quiet respiration.

The ballistocardiograph was a modified direct-body electromagnetic pick-up type as previously described.[13] The frequency response of the filter-oscillograph system was determined by introducing a square wave signal in series with the pick-up coil and was found to give an essentially straight line response from 1 to 12 cycles per second to the voltage input. The ballistocardiogram recorded with this transducer and filter system was neither velocity nor displacement, but intermediate and lagged a pure velocity ballistocardiogram by 45 degrees. Standardization from subject to subject was kept constant by fixing the gap from coil to magnet at 10 mm. and maintaining the sensitivity of the galvanometer response at 10 mm. for 1 mv. This type of ballistocardiograph may be expected to yield completely reproducible tracings when used under the conditions of standardization described. Lead I of the electrocardiogram served as a timing reference for the ballistocardiogram.

The amount of damping in a system may be measured by the principle of determining the rate of decay of oscillation in the system and expressing this as the logarithmic decrement.[14] This was determined by recording the movements of the body subsequent to displacing the subject from the resting position by pushing the right shoulder and suddenly releasing the body. The sensitivity of the recorder had been attenuated until no deflections were inscribed by the cardiovascular forces. The damping factor was determined by measuring the ratio of the amplitudes of two successive waves after the tap.[15] Body frequencies were also measured.

The age, height, weight and body surface area of each subject were noted. The ideal weight according to age and height was determined from the normal standard tables and the deviation from the standard of each subject was calculated. In addition, the decay curve of body oscillation of 35 unselected subjects of this group was determined by the method described above, in various phases of respiration. Thus the body damping and frequency response were studied and compared during normal quiet respiration, held deep inspiration and held deep expiration.

Results

Ballistocardiograms were graded normal, borderline, or abnormal.[4] In the 15 to 30 year age group, 6.8 per cent of the subjects had abnormal tracings, with a similar number judged borderline. In the 31 to 45 year age group, 12.5 per cent had abnormal tracings, with a similar number judged borderline. In the 46 to 76 year age group, 25.6 per cent of the subjects had abnormal tracings, with 20.5 per cent judged borderline (table 1).

Table 1.—*Relationship of Abnormal Ballistocardiograms to Age, Male and Female*

Age	No. of Subjects	Borderline		Abnormal	
		N	%	N	%
15–30	(29)	2	6.8	2	6.8
31–45	(32)	4	12.5	4	12.5
46–76	(39)	8	20.5	10	25.6

Table 2.—*Age and Body Measurements of Subjects*

	Height		Weight		Age		Body Surface Area	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Male (63)	65.7	3.42	151.6	20.32	44.5	15.85	1.79	0.15
Female (37)	62.8	5.48	120.5	31.54	37.1	13.89	1.57	0.15
Combined Male & Female (100)	65.3	3.87	139.78	33.63	41.84	15.36	1.71	0.15

Table 3.—*Means, Standard Deviation and Standard Error of Mean of Body Frequency and Damping*

	Body Frequency*			Body Damping†		
	Mean	S.D.	S.E.M.‡	Mean	S.D.	S.E.M.
Male (63)	3.67	0.92	0.12	3.25	1.72	0.22
Female (37)	3.80	0.76	0.13	2.49	0.76	0.13
Combined Male & Female (100)	3.72	0.86	0.09	2.97	1.51	0.15

* Cycles per second.
† Lobe ratio.
‡ Standard error of the mean.

Mean ages and body measurements of the subjects are presented in table 2. Males averaged 7 years older, 3 inches taller and 31 pounds heavier than females, with corresponding differences in body surface areas. Mean body frequencies of both male and female subjects varied little, with only small differences between the two sexes. On the other hand, body damping was greater in the male than in the female with mean body damping coefficients of 3.25 and 2.49, respectively (table 3).

Relationship between age and body measurements to body frequency and damping: Correlation coefficients between age and body measurements with body frequency and body damping are listed in table 4. There was

TABLE 4.—*Correlation Coefficients Between Age, Body Measurements and Body Frequency and Damping*

	Female N = 37		Male N = 63		Combined Male & Female N = 100	
	Body Frequency*	Body Damping†	Body Frequency*	Body Damping†	Body Frequency*	Body Damping*
Height	−0.15	0.09	−0.13	0.19	−0.11	0.11
Weight	−0.11	0.01	−0.31	0.25	−0.15	0.11
Age	0.14	0.63	0.085	0.74	0.09	0.71
Body Surface	−0.21	0.07	−0.15	0.25	−0.11	0.31
Body Damping	0.42		0.09		0.22	
The significance of the correlation coefficients at					5%	1%
for N = 37					0.32	0.42
N = 63					0.25	0.32
N = 100					0.19	0.25

* Cycles per second
† Lobe ratio.

TABLE 5.—*Effects of Age on Body Frequency and Damping*

	Body Frequency*			Body Damping†		
	Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.
Age 15–45 years						
Female (30)	3.68	0.68	0.124	2.29	0.76	0.138
Male (30)	3.67	0.83	0.151	2.66	1.36	0.248
Combined Male & Female (60)	3.67	0.78	0.100	2.47	1.13	0.145
Age 46–76 years						
Female (7)	4.33	0.67	0.252	3.34	0.85	0.328
Male (33)	3.70	0.87	0.151	3.80	1.81	0.314
Combined Male & Female (40)	3.81	0.92	0.145	3.72	1.69	0.266

* Cycles per second.
† Lobe ratio.

significant correlation between age and body damping. Correlation coefficients between body damping and body frequency with body measurements were below the level of significance. Body frequency showed no significant correlation with body damping in the group of males and only borderline correlation at the 1 per cent level of significance in the group of females.

In order to better evaluate the effects of age on body frequency and body damping the series was divided into two groups, namely: those between 15 and 45 years of age and those between 46 and 76 years of age. The means and standard deviations of body frequency and body damping for these two age groups are listed in table 5. Mean body damping of the older age group was significantly higher than that of the younger age group. However, the mean body frequency of each of the two groups did not differ significantly. Application of the "*t* test"[16, 17] for the significance of these differences is noted in table 6.

TABLE 6.—*Significance of Difference Between Means of Body Damping and Frequency in Subjects 15 to 45 Years of age and those 46 to 76 Years of Age*

Item	*t* Value Found for Female (15–45 yrs.) Vs. Female (46–76 yrs.)	*p* Significance	*t* Value Found for Male (15–45 yrs.) Vs. Male (46–76 yrs.)	*p* Significance	*t* Value for Female & Male (15–45 yrs.) Vs. Female & Male (46–76 yrs.)	*p* Significance
Body Frequency*	2.21	.02	0.14	.90	0.82	0.9
Body Damping†	3.00	.001	2.85	.001	4.17	.001

* Cycles per second.
† Lobe ratio.

The effects of deviation from "ideal weight" on body frequency and body damping: The subjects were considered in four groups: Group 1, "ideal weight" ±9 per cent; group 2, "overweight" 10 to 25 per cent; group 3, "underweight" 10 to 19 per cent; and group 4, "underweight" 20 to 29 per cent. Table 7 summarizes the means and standard deviations of the four groups in regard to age, body damping and body frequency. There was no significant difference in the mean ages of the four groups. Likewise, there was no significant difference in the mean body damping of the four groups. Body frequency was definitely higher in those subjects who were 20 to 29 per cent below "ideal weight." Body frequency was lower in those subjects who were 10 to 25 per cent above "ideal weight." Application of the "*t* test" for the significance of these differences is noted in table 8.

TABLE 7.—*Effects of Overweight and Underweight on Body Frequency and Damping*

	No. of Subjects	Age			Body Damping†			Body Frequency*		
		Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.	Mean	S.D.	S.E.M.
±9% Ideal Weight	(48)	39.6	14.44	2.08	2.91	1.48	0.21	3.72	0.74	0.11
10–25% Overweight	(18)	43.8	16.53	3.89	2.89	1.58	0.37	3.28	0.40	0.09
10–19% Underweight	(17)	42.6	16.61	4.03	3.01	1.25	0.30	3.84	0.74	0.18
20–29% Underweight	(17)	45.05	15.09	3.63	3.26	1.54	0.37	4.12	1.01	0.24

* Cycles per second
† Lobe ratio

TABLE 8.—*Significance of Difference Between Means of Body Damping and Frequency in Groups of Subjects that are of Ideal Weight, Underweight and Overweight*

	t Value Found for Ideal Weight Vs: 10–25% Overweight	*p* Significance	*t* Value Found for Ideal Weight Vs: 10–19% Underweight	*p* Significance	*t* Value Found for Ideal Weight Vs: 20–29% Underweight	*p* Significance
Body Damping†	0.05	0.09	0.27	0.8	0.83	0.4
Body Frequency*	3.38	0.001	0.60	0.5	1.53	0.1

* Cycles per second.
† Lobe ratio.

TABLE 9.—*The Effect of Respiration on Body Frequency and Damping (35 Subjects)*

	Normal Respiration		Deep Inspiration		Deep Expiration	
	Body Frequency*	Body Damping	Body Frequency*	Body Damping†	Body Frequency*	Body Damping*
Mean	3.35	3.98	3.28	3.56	3.47	3.86
S.D.	0.84	1.89	1.32	1.52	0.82	1.73
S.E.M.	0.198	0.445	0.311	0.358	0.193	0.408

* Cycles per second.
† Lobe ratio.

The body frequency and damping of 35 of the subjects were determined during normal quiet respiration, deep held inspiration and deep held expiration. The results are listed in tables 9 and 10. No significant difference was noted in body frequency or body damping during any phase of respiration.

TABLE 10.—*Significance of the Difference betwene Means of Body Frequency and Damping during Normal Respiration, Deep Inspiration and Deep Expiration*

	t Value Found for Normal Respiration Vs. Deep Inspiration	*p* Significance	*t* Value Found for Normal Respiration Vs. Deep Expiration	*p* Significance
Body Frequency*	0.46	0.6	0.024	0.9
Body Damping†	0.72	0.4	0.20	0.8

* Cycles per second.
† Lobe ratio.

DISCUSSION

In the production of the ballistocardiographic record the forces generated by the cardiovascular system are impressed on the body mass which has complex couplings, damping resistances and various mechanical impedances to the transmission of these forces to the surfaces of the body. This results in considerable distortion of the ballistocardiogram both as to the contour and phase of the various waves and segments. The concept of Von Wittern[11] and Reissmann and Dimond[18] of dividing the body into an external and internal network contributes to the understanding of the various mechanical damping factors.

Ballistocardiograms in our series in the younger age group whose body damping factor was low had a definite oscillatory pattern. There were exceptions in four young individuals. These four all had abnormal ballistocardiograms, but their body damping factor was found to be high and in the range usually observed in much older individuals.

The data in this report indicate that the damping of the body shows definite variation with age. On the other hand, weight, height and body surface areas did not show any significant correlation with body damping. The correlation of high degrees of body damping with increasing age may be of importance in explaining the greater number of "abnormal"

ballistocardiograms which are encountered among "healthy" older individuals.[20]

Our data further indicate that body frequency is quite constant and does not vary with age, sex or normal range of body measurements. However, overweight tends to decrease the natural frequency of the body and underweight tends to increase the natural frequency of the body.

Distortion of the ballistocardiogram may be due to variation in the frequency of the impressed force, the circulatory apparatus, the natural frequency of the vibrating mechanical mass, the body, or the frequency response of the recording system, transducer-filter-oscillograph. The ratio of the frequency of the impressed force to the natural frequency of the body is a factor in tachycardias where the ratio of the two frequencies is such that there may be accentuation of the resultant ballistocardiographic waves due to resonance.

It becomes apparent that the damping and frequency response of the body mass is of considerable importance in the present methods of recording the force of the heart by the ballistocardiograph. In order to record the true ballistocardiographic waves one must control the large variable of body damping. If the damping of either the body or the associated recording system be altered so that the overall damping is made constant at some optimum level, then a more accurate registration of the cardiac forces will become possible. The use of a critically damped, low frequency table or an aperiodic system approaches such an ideal. A direct body ballistocardiograph can be used for recording a "true" or undistorted tracing by changing the surface upon which the body lies or the application of sandbags to the subject which effectively changes the body damping.[7] The direct body ballistocardiograph may also be utilized in conjunction with an electronic system designed to "smooth out" these factors of frequency and damping and thus approach a "true" force curve.[19]

In ordinary clinical use however, from the data presented in this report, one could record the oscillatory decay curve of the body after each tracing and make suitable allowance for unusual variations in body damping or frequency, in the clinical interpretation of the ballistocardiogram.

Summary and Conclusions

1. The natural frequency of the body and body damping of 100 normal subjects were studied for their effects on the ballistocardiogram.

2. After an impressed external force the oscillatory decay curve of the body was measured.

3. A standard statistical analysis of the results showed that body frequency was not correlated to age or normal anthropometric measurements.

4. Body damping correlated significantly with age but not with normal body measurements.

5. Overweight and underweight affected body frequency but not body damping.

6. Respiratory variations did not significantly modify body frequency or body damping.

7. There was no significant correlation between natural body frequency and body damping.

8. It was suggested that truer recording of the cardiovascular forces by the ballistocardiogram could be obtained by adjustments of apparatus to make allowance for variations in body damping.

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CLINICAL CONFERENCE

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Rehabilitation of the Cardiac Patient

By EDGAR DURBIN, M.D., AND LEONARD J. GOLDWATER, M.D.

REHABILITATION of the cardiac is one of the most important problems that confronts the American medical profession today; when it is ideally handled every doctor will understand how to return his cardiac patient to work as soon as possible. It is estimated that some 800,000 Americans die per year of heart disease and that there are about 10,000,000 living Americans with heart disease. Because of this, incalculable numbers of work days are lost with loss of productivity amounting to several billions of dollars. The problem will not become less inasmuch as 8 per cent of the population are now over 65 years of age, and by the year 2000, it is estimated that 13 per cent of the population will be over 65 years.

It is interesting, in this period when cardiac work classification clinics are being set up and rehabilitation conferences are being held, to reflect that the first cardiac clinic in the U. S. was established at Bellevue Hospital, New York, in 1911, as a Social Service Cardiac Clinic for Working Adults.[1] In 1941 the first Work Classification Clinic Unit was started there. The Altro workshop, organized originally 35 years ago to aid tuberculous patients, started admitting cardiacs in 1948. The Cleveland Work Classification Clinic was started in 1949. In 1954, there were about 30 cardiac work classification clinics in the country, and the American Heart Association set up a Rehabilitation Committee to work on the problem of rehabilitation of the patient with heart disease.

At the first (1950) National Conference on Cardiovascular Diseases, rehabilitation was defined as "the return of the person disabled by accident or disease to his greatest physical, mental, emotional, social, vocational, and economic usefulness, and if employable, an opportunity for gainful employment". Rusk states that the objective of rehabilitation is to "retrain the individual to live within the limits of his disabilities but up to the hilt of his capabilities." Plummer[2] has said "no patient is well until he returns to his regular occupation, or when necessary to another for which he is fit both physically and psychologically." Rehabilitation may be simply defined as "from bed to job."

Quite often the "rehabilitation" of the cardiac consists in rehabilitating somebody who thinks he has heart disease, but actually does not. Goldwater[3] found that 28 per cent of the patients referred to the Bellevue Work Classification Unit had no heart disease. The Pittsburgh clinic has recently reported that 25 per cent of their first 335 cases, referred mostly by private practitioners, had no heart disease.[4] The experience of the Cleveland Classification Clinic is similar in that anxiety and tension were found to be the most important factor in almost one half of their cases.[5]

Many articles have been written about iatrogenic heart disease.[6] It is still prevalent, and will undoubtedly not decrease until the medical profession realizes the factors that lead to it. Undue attention to physical findings, as in taking the blood pressure, listening to a fast heart, shaking one's head when irregularities are present, or undue attention to murmurs, particularly if the individual is unaware of their presence, lead to the belief that something is wrong with the heart, and this may lead to a feeling of disability. Re-examinations

This article had been begun by Dr. Durbin but was not completed because of his death. The manuscript was prepared for publication by Dr. Leonard J. Goldwater.

of the patient without an explanation of the reasons for these re-examinations are pernicious in their effect on the patient.

Quite often the medical practitioner fails to correlate the symptoms with signs, and if the examination is incomplete and does not include necessary laboratory procedures, a practitioner may be led to believe that certain abnormalities of the heart, as for instance innocent murmurs and a slightly elevated blood pressure, may be the reason for the patient's symptoms.

If a person has heart disease, and the doctor advises the patient to "take it easy," the patient often feels that he must do practically nothing. At other times the use of digitalis or nitroglycerin or a salt free diet may make the patient feel that the heart disease is more serious than is actually true.

Not infrequently, the practitioner advises the individual with heart trouble to change his job or to sell his business because he has had symptoms of heart disease. This may lead to considerable mental anguish and, at times, serious financial upheaval.

There are many factors that influence the employment of cardiacs. Perhaps the most important is his mental attitude. He must understand his cardiac condition, and then, according to Pinner, he must accept reality regarding this condition, otherwise he cannot be properly placed in industry.[7] It is essential that he hopes to be relatively well and believes that his condition will improve. He must have pride and the desire to better himself by working.

It has been the experience of the Work Classification Clinic of the Colorado Heart Association that the influence of public welfare funds on the desire to work has been considerable. Although welfare departments have a great interest in rehabilitation, their help should be balanced by other kinds of help in order to keep alive in the disabled individual a desire to earn a livelihood and remain a confident citizen. As the resident physicians of the charity hospitals have become conscious of our aims and the difficulties surrounding return of the cardiac to work, they have brought to the clinic patients in the earlier stages of convalescence before welfare funds have had their influence in increasing the deterioration of ambition. Recently, our cases have been more interested in returning to work.

Likewise, disability insurance benefits and prolonged litigation may have an effect on the cardiac as well as on those with other illnesses. If people do not work for two years, they have a very bad prognosis for future employment.

Next to the mental condition is the physical condition itself. This varies considerably depending upon the etiology as well as the severity of the heart disease. Patients with rheumatic mitral stenosis get short of breath more easily than patients with other types of heart disease, and this symptom slows them up even though they are quite ambitious. On the other hand, rheumatic or syphilitic aortic regurgitation may lead to much more enlargement of the heart and yet symptoms may occur late. Hypertensives do well until such time as they connect headache and other symptoms with the accidental finding of high blood pressure. When dilatation occurs, of course, hypertensives fall into the same class as other cases of congestive heart failure. Arteriosclerotics may show the symptomatology of angina or of congestive failure depending upon the stage of their progression. The important part for the medical profession to realize is that pain in the chest is not necessarily due to coronary insufficiency. Even when a person has had a myocardial infarction, the chest discomfort that is often complained of may not be due to the underlying coronary artery disease, but due to anxiety. Another thing to remember is that even in the presence of angina pectoris, moderate unhurried activity is possible, and this is consistent with many types of work. Even congenital heart disease characterized by marked cyanosis is compatible with a fairly normal adult life.

Working conditions have some influence on employment of cardiacs. Ventilation, temperature, light and the height of benches at which work is performed all have an influence. In certain industries, the machinery is so hazardous that cardiacs subject to loss of equilibrium or loss of consciousness cannot be used. Cardiacs can do considerable work if they are

not called upon to work too fast with heavy loads. The speed of movement is important, and in those who are very seriously handicapped, quick assembly line procedure may not be suitable. Another factor that may influence the cardiac adversely is nervous tension. The attitude of a foreman may have an important bearing on whether or not a cardiac can carry on his work.

Travel to and from work, home conditions, union seniority rules, workmen's compensation laws and the state of the labor market are other factors that bear upon the occupational potentialities.

Bielawski,[8] who has worked considerably with individuals in large industries, has stressed the fact that there must be a definite understanding between the personal physician and the industrial medical director, or between the physician and the general manager of a company in order that a cardiac can be properly placed. It is helpful if physicians are intimately informed as to the actual work operations of an industry.

Cardiacs have been able to work very effectively and, according to Stroud,[9] are appreciative of their employment, faithful and steady. This fact is attested to by many physicians who work with some of the leading industrial enterprises of the country.

A PHYSICIAN: Is there anything known about the effects of continuing to work on the subsequent course of heart disease? In other words, might it shorten life or lead to complications?

DR. DURBIN: The effect of employment on the patient has been studied by various doctors. Goldwater and his associates analyzed 580 clinic cases that had been known cardiacs for 5 to 15 years.[10] Of these, 81 per cent were working and 19 per cent were not. Over a period of time, the functional capacity diminished more in the nonworking cases than in those who had continued working and episodes of congestive failure, myocardial infarction, acute rheumatic fever, cerebral accidents occurred in 30 per cent of those employed and 34 per cent of those unemployed. These episodes occurred in 179 of the 580 cases studied. It was concluded that "there is no evidence in this study that continued employment had an adverse effect on the course of heart disease." Stroud[9] felt that infections play a larger part in cardiac failure and the progression of cardiac disease than physical effort. Experience of the Cleveland Area Work Classification Clinic[11] and that of the Western Pennsylvania Heart Association is similar to that of Goldwater. The former found that there was an improvement of the cardiac status more commonly than deterioration. The latter felt that 73 per cent of those working were not harmed by the employment.

A PHYSICIAN: What are the chances of a patient being able to return to work following a severe cardiac episode such as a coronary occlusion, rheumatic activity and so forth?

DR. DURBIN: Most of our figures with respect to the return of cardiacs to work concern those with coronary disease. Goldwater[12] found that after coronary occlusion 74 per cent returned to full time, 14 per cent returned to part time. Crain[13] and his associates reported that after myocardial infarction 78.8 per cent resumed work. Kaufman[14] states that 75 per cent of those who recover from myocardial infarction are re-employable. Weiss and Gray[15] agree with the 75 per cent figure. Master[16] reported 53 per cent of those who had coronary occlusion resumed work. Sprague[17] found that 80 per cent of cases with myocardial infarction returned to work. The Metropolitan Life Insurance Company has found that many cases of coronary occlusion were working to full capacity 10 years after an occlusion. Levine and Phillips[18] found that 56 of 84 cases with myocardial infarction returned to work, and 30 were still working at the end of one year; one half of these were manual laborers. This agrees with the early Bellevue experience that those who presumably were least able, were doing physical work of unskilled type. In a study of those with congestive failure, Master[16] reported that 68 per cent returned to full time, 19 per cent returned to limited work.

A PHYSICIAN: What types of cardiac cases should not be permitted to do any work at all?

DR. DURBIN: The profession is too impressed with the fact that certain stages of heart disease do not permit work. It is true that

acute rheumatic fever, acute hypertensive crises, acute myocardial infarction, subacute bacterial endocarditis, acute congestive failure from whatever etiologic cause, beriberi heart, acute cor pulmonale, certain arrhythmias such as atrial fibrillation, flutter, atrial tachycardia, ventricular tachycardia or fibrillation, A-V nodal tachycardia do not permit continuing with a job. A good many cases of heart block cannot work. When heart disease is complicated by profound anemia or there is a status anginosus, a job is very difficult to hold. Certain congenital anomalies are not consistent with employment. Marked hyperthyroidism or myxedema if untreated is likewise not consistent with work.

However, most cardiacs can work, and there are certain types of heart disease that are reversible and so permit good function after the acute phase. Rheumatic heart disease without residuals or with minimum residuals may not prevent a fairly normal life afterwards. This can be illustrated by the case of F. K., a girl of 15, who was seen first in Sept. 1952. At that time she had acute rheumatic fever with carditis and congestive failure. From early November until two weeks before Christmas she was in an oxygen tent and was treated with digitalis and the usual diuretic drugs and low salt diet. Finally the rheumatic fever burned itself out, and she was able to be up without oxygen and was able to go home for Christmas. When last seen she was attending school, was active and leading a normal life except for competitive sports.

Another case is that of E. L., a girl of 16, who was seen first following a cerebral episode. Diagnosis of coarctation was made because of the characteristic findings. She was operated on by a well-known surgeon in Chicago and the next year returned to school. She has had no further symptomatology of coarctation, and has gone through technical training at the University of Colorado Medical School and served as an x-ray technician in that busy department.

Hearts affected by thyroid disease can now be treated with propylthiouracil, iodine, and surgery. The symptomatology of arrhythmias and congestive failure are well controlled. People affected by myxedema can be controlled for long periods of time with thyroid preparations. I recall the history of a woman of 52 who was one of the first patients treated with thyroid gland before the days when potency could be definitely measured. She had a blood pressure of 300 mm. Hg at times and yet lived to the age of 90. Other types of reversible heart disease are beriberi heart amenable to treatment with B_1 vitamin, constrictive pericarditis which can be corrected surgically, and acute cor pulmonale, which if not fatal, very rarely leaves residuals.

Many types of heart disease, although not reversible, are much improved after treatment, and permit employment on a job with decreased physical work or decreased mental strain. J. C., an engineer on C. B. & Q Railroad suffered a myocardial infarction in Oct., 1947. Following hospitalization and treatment, he returned to work in March, 1948. Since then he has been working actively on the line, and has had no subsequent recurrence. D. T., banker and public figure, suffered a mild myocardial infarction in August, 1950. When last seen in Feb., 1954, he was hale and hearty and asymptomatic. He is traveling frequently by air and train all over the country. H. H., a practicing physician in the eastern part of Colorado, suffered a myocardial infarction in Dec., 1948. He returned to work and tried to modify his general practice, taking a course in ophthalmology, and then because of pressure returned to general practice. On a South American cruise in August, 1952, he suffered a second myocardial infarction which was less severe and he returned to this country. On advice he has been on anticoagulant therapy from that time on. He is at present engaged in the general practice of medicine.

A PHYSICIAN: Does an episode of congestive failure preclude future employment?

DR. DURBIN: Congestive failure does not mean that the individual, who first suffers this, is completely shelved, but on the contrary, many people who suffer their first congestive failure can, with various drugs, lead a normal life thereafter for many years. The simple use of digitalis is often enough to take care of this failure and control atrial fibrillation, which

is often a cause for the failure. Many individuals need various diuretics in addition to digitalis, but these are easily administered. Most simple is ammonium chloride, the only deterrent being the number of tablets necessary for effective diuresis. Oral mercury is now available in effective preparations, and can be bolstered by periodic intramuscular or subcutaneous injections of mercury. We must not forget the effectiveness of theobromine, theophylline, caffeine and the new preparation Diamox (acetazoleamide).

A. H., a man of 47, was found on routine examination to have a greatly enlarged heart. However, he had very little symptomatology until at the end of a summer vacation, when he developed signs of congestive heart failure and pulmonary edema. He was hospitalized when it was found that he had developed atrial fibrillation. With digitalis and quinidine he was restored to normal function, and since then, with the exception of one recurrent spell of congestive failure, has been continuing in his employment as a draftsman for the U. S. Geological Survey.

Even cases showing arrhythmias can remain employed if adequately treated. D. C. had noticed that he had lost strength and energy, and was unable to work as a heavy-machine operator. Because of the recent symptoms it was suspected that myocardial infarction was responsible for the complete A-V block which was present. However, serial electrocardiography indicated that this was not so. Consequently, he was put on a regime of weight reduction and Paredrine, and after the loss of weight, even though the arrhythmia was not influenced by the Paredrine or adrenalin or other drugs, he has been able to work as a heavy-machine operator and claims that he has never felt better in years.

A PHYSICIAN: Have you had any experience with employment following commissurotomy?

DR. DURBIN: I can best illustrate this by citing the case of S. T. who first noticed shortness of breath in 1940 when she was 19 years old. Subsequently she had several periods of congestive failure and showed progressive diminution of cardiac reserve due to mitral insufficiency and stenosis. Following a commissurotomy in July, 1953, she was able to resume full household activity including cooking, cleaning, laundry and shopping.

A PHYSICIAN: What kinds of jobs can cardiacs do?

DR. DURBIN: That's quite a question. In Philadelphia, 40,000 workers were studied and it was found that there were 1,000 operations in 25 industries suitable for cardiacs. It was concluded that 25 per cent of all jobs in industry are possible of performance by cardiacs without compromising the job or the worker. These investigators felt that almost 100 per cent of cardiacs outside of class IV (congestive failure) were employable. Harvey and Luongo[19] found that 1268 jobs out of 5100 studied were suitable for people with compensated heart disease. They felt that the two most important factors in estimating physical capacity for work were the diagnostic acumen of the examining physician and his knowledge of industrial condition. In the placement of cardiacs, Sprague[17] advised against jobs that entailed exposure to upper respiratory infections, heavy lifting, working with arms overhead, crawling, pulling, climbing, dangerous machinery, cold temperatures and work done at other than the speed determined by the individual. The War Manpower Commission warned regarding the use of hypertensives in occupations involving work in high or cramped places, in great heat, and for activities related to dizziness (stooping, climbing, crouching, kneeling, balancing, throwing, turning, crawling, jumping). Work involving the safety of other people or of valuable property should be avoided. Benton and Rusk[20] warned against using those individuals with significant aortic or mitral stenosis in jobs where public safety might be endangered by sudden syncope of the individual (public transportation, window cleaning and other scaffolding jobs).

A PHYSICIAN: How do you know when a cardiac is ready to return to work?

DR. DURBIN: Weiss and Gray[15] studied 344 myocardial infarctions who returned to work within three months. Master[16] studied 422 ward and private patients, and of these 53 per cent returned to work, the majority to

full time work. Ninety-two per cent of this number returned within one year. The younger the patient, the more likely the patient was to return to work. One half returned to work in three months, three quarters returned to work within six months. As to the type of work, one half of the laborers returned to work, two thirds of the white collar and office workers returned to work and four fifths of the professional people.

A PHYSICIAN: Are cardiac function tests of any value in deciding what kind of work a man can do?

DR. DURBIN: At present, advice regarding employment depends on the knowledge and application of the New York Heart Association nomenclature[21] pertaining to functional capacity of the heart and on clinical judgment based mostly on history given by the patient. Goldwater[22] has pointed out that "in estimating work capacity, as in other fields of medicine, there is probably no substitute for clinical judgment based on careful observation and experience." In an attempt to sidetrack this clinical judgment, various function tests have been proposed. At present there is a difference of opinion regarding their value. Warren[23] states that there are, at present, no reliable tests and that history and judgment are still best. Goldwater[22] feels that available tests are of little or no value in assessing work tolerance in a specific job. Pordy, Master and Cheskey[24] feel that the two-step test is valuable and better than the anoxemia test. They state that a normal ballistocardiogram in a person over 50 years of age is significant and that a ballistocardiogram that is abnormal in a person under 50 is significant. Their experience has shown that an abnormal ballistocardiogram occurs in 93 per cent of anginal patients with abnormal electrocardiograms and that the resting ballistocardiogram is abnormal in 85 per cent of individuals who have angina and normal resting electrocardiograms, but abnormal two-step electocardiograms. These tests, however, merely reflect cardiac reserve and hence have only indirect value in determining employability.

It may be fairly stated that no single physical finding or test is a prognosis for work. Blood pressure is a general reflection of the strength of the heart to perform exercise, and yet in some cases, it does not properly measure the ability of an individual to carry on. In general the pulse is a measure of the cardiac reserve; the faster the pulse the less able the heart to perform work. In general the heart size is a reflection of cardiac reserve. When a heart is enlarged, it is generally less able to perform work than that of the individual with a normal size heart.

An electrocardiogram may indicate very serious heart disease, and yet the residuals of myocardial infarction are not enough to contraindicate regular moderate exertion.

Observation of an individual during an exercise test may give some indication of how that individual responds to exercise but Lewis pointed out there is no way to test the heart by examination except to observe how the exercise is performed and its results on the individual. On the other hand, when a Master two-step test is positive, it is probably inadvisable to assign the individual concerned to severe exertion. The same may be said for vital capacity.

Eggleston has said that the tests are valuable objectively, but merely corroborate clinical experience and good clinical judgment, and Sprague[17] feels that the best way to evaluate a cardiac is to determine the heart size and whether dyspnea and angina are present when the patient is ambulant.

A very important evaluation of the cardiac pertains to his attitude and his beliefs. Benton and Rusk[20] have pointed out the frequency with which disabling cardiac neurosis (superimposed on nondisabling cardiac disease) is met within the cardiac clinic. This is one of the greatest obstacles to the rehabilitation of the cardiac patient. I again refer to the experience of Goldwater[3] at Bellevue that 28 per cent of his clinic patients had no organic heart disease, and the other figures of the Pittsburgh clinic.[4]

A PHYSICIAN: How can the doctor assist in returning his patient to work?

DR. DURBIN: The doctor must show confidence in his diagnosis, treatment, and prognosis. He must explain the patient's condition

to him, and explain his projected treatment early in the course of the illness. He must also explain the prognosis, and should be hopeful in his attitude, stressing the best sides of the prognosis to the patient in order that he may not feel that he is "on the shelf." In his visits to the patient, repeated encouragement is advisable and pays dividends. In this encouragement, examples of recovery help the patient, who, because of his personal problem, has not had time to compare his predicament with that of individuals he knows who have recovered. The testimonial technique is beneficial. He should be advised to look back one or two weeks rather than one day in order to see that he is recovering, and is much better off than he was when the illness started.

His stages of improvement should be dramatized to him. Successive "graduation" from oxygen tent, salt-free diet and diuretics can be pointed out as concrete evidence of improvement.

The patient should be warned about symptoms of weakness, sweating and perhaps temporary palpitation and shortness of breath. It should be called to his attention that sitting in a chair is not ambulation and that sitting is an act that does not lead to the acquisition of strength. Using one's feet and legs strengthens them, and is the best all around conditioner. It is essential that short walks be taken with necessary rest periods, but it is important to impress on the convalescent person that the exercise itself is the beneficial part of convalescence and that the rest periods are only subsidiary. A few steps from bed to chair are increased in frequency, and then the number of steps from bed to bathroom, and from bed to hallway, and up and down the hallway are increased and the length of rest periods are decreased. With increased exercise, the individual soon acquires the sense of well being, and at this time should think about the return to work and its responsibility.

In order to evaluate properly a patient's response to exercise and to give a prognosis with respect to reconditioning and return to work, the doctor must see the patient frequently. As soon as possible after discharge from the hospital or from bed at home, it is well to have the individual report to the office. The simple chore of expending energy in going to the office is beneficial, and, in addition, gives confidence to the patient that he is doing more than he has done for some time. If tolerated well, it furnishes the basis for encouragement by the doctor, and if productive of symptoms, it enables the doctor to treat the patient further in the same manner or by additional therapeutic methods. Laboratory procedures such as electrocardiogram, x-ray films, blood counts and sedimentation rates give an additional measure of the patient's condition and serve as a basis for further instruction by the doctor. These repeated examinations should be conducted at increasingly longer intervals, and thereby serve to encourage the patient to live a more normal life than he has during his acute illness.

The family physician must be thorough in his analysis of the individual and his complexities of life. He must take the time to inquire into the patient's family, his job and what he does, his clubs and associations, his church affiliations, how far he has to drive in going to work or how long he has to stand hanging onto a strap. He must understand the social excitement, the desire to play poker or bridge. He must look into the sexual life of the individual, and if female, must inquire with respect to the chance of pregnancy (Kaufman permits intercourse six to eight weeks after a myocardial infarction). The personal habits of an individual with respect to the use of caffeine-containing beverages, the use of alcohol and the use of tobacco all have a bearing on how the individual is instructed to live after a bout of cardiac disability. A person's previous hobbies, particularly physical pursuits such as golf, gardening, fishing, hunting, bowling and so on must be taken into account.

A simple dictum "take it easy" is not enough. This advice too often leads to anxiety and insufficient exercise to maintain good physical condition.

The family physician must recognize that

continued regulation is necessary for good prognosis, and it is well for him to explain this to the patient. Regular examination by means of the usual physical examination, x-ray films at six feet and electrocardiograms will help to furnish the basis for the doctor's advice regarding the individual's activity.

If properly prepared by the doctor as to what to expect, the cardiac can expect to continue in good health for a long period of time. Incidentally, the American Heart Association has published a very useful booklet[25] to guide physicians in returning cardiacs to work.

The physician should recognize that an early return to work has a tonic effect on the person who has been sick. On the other hand, he should realize that the feeling of disability becomes a habit because of neurogenic overlay, and the general feeling that rest is beneficial. However, to combat this, it is essential that the doctor should repeatedly emphasize that the necessity for rest is a temporary measure in order to allow the heart to overcome the injury produced, and that after this temporary rest, activity is essential in order to gain strength.

Various things complicate return to work. When an individual has a serious illness, all too frequently public relief agencies mercifully take care of the individual and his family, but sometimes this is so adequate that the return to work at a lower wage figure seems impossible to the sick patient. Only ambition and pride can offset the effects of this help. Another factor that works against an individual returning to work is the possession of disability insurance. It is a natural reaction for the sick individual to feel grateful that he has had such foresight to provide for his care during an illness and grateful that he has this feeling of security. Not knowing his future possibilities, he is inclined to depend upon this security rather than give it up. The cost to the taxpayers is considerable because of this attitude on the part of those who are sick.

Prolonged rest is harmful because muscular tone decreases any effort, leads to symptomatology which is ascribed to heart disease rather than to the lack of muscular tone and a vicious circle is set up. If an illness is kept short by the help of the doctor, employers are more cooperative in using again the employee who has been sick. The family exchequer is harmed less and the discouragement of the individual is avoided. With prolonged illness the individual loses spirit and with continued weakness this continues.

What then should be our objectives with respect to rehabilitation of the cardiac? An early diagnosis is essential. This gives the basis for treatment which should be instituted at once and explained to the patient. The doctor, nurse and social service worker can collaborate in doing the best job for the individual. With individualization, vocational planning may be carried out early and the results be more effective than if it is delayed until the cardiac has been put in a rut of difficult living. Early counseling in a clinic, in conjunction with those interested in vocational rehabilitation, is advisable. Health agencies can be called upon to do their bit by referral to various services available in the community. The State Department of Education can help in the training of rheumatics or in modifying the employment of hypertensives and arteriosclerotics. Welfare agencies, if they understand the problem, can better help in temporary assistance and encouraging the sick individual to return to a wholesome, independent way of earning a living for himself and family. A realization by the medical profession that the follow-up care is a doctor's responsibility, and that he can assist considerably by giving definite appointments for re-examination, will help considerably in proper placement of the cardiac in industry. It is essential that patients be encouraged to get back to work as early as possible, and thus forego the time-honored remedy of taking a rest. It must be remembered that the laity do not understand heart disease and that it must be explained to them. This necessitates the doctors taking time to talk to the patient. In so doing, they will cause less iatrogenic heart disease than has been prevalent in the last decade and it may even be possible to promote the employment of cardiacs who are

55 years of age and older. This is essential, inasmuch as we are going into an era of older people in our civilization.

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CLINICAL PROGRESS

Respiratory Insufficiency and Chronic Cor Pulmonale

By IRVING MACK, M.D., AND GORDON L. SNIDER, M.D.

THIS article attempts to apply the new knowledge of cardiopulmonary function to a clearer understanding of the pathophysiology, diagnosis and therapy of respiratory insufficiency and chronic cor pulmonale. The reserves or margin of safety of pulmonary function are very large. Thus, the normal untrained individual can increase his oxygen uptake and ventilation to approximately 10 times the resting level before exhaustion supervenes. Even at this point the respiratory reserves are not exhausted, because the ventilation at exhaustion is usually not more than half of the maximum breathing capacity. The capacity for work in the healthy individual is limited by the cardiocirculatory system rather than by the respiratory system. The ease with which pneumonectomy is tolerated, when the contralateral lung is normal, is a direct demonstration of this fact. It is not surprising, therefore, that severe degrees of respiratory dysfunction may be present without disability or respiratory insufficiency.

Chronic pulmonary disease and chronic cor pulmonale are more frequent in industrial urban centers, particularly in the north temperate regions, among laborers, and in mining regions. Fulton[1] states that in Manchester, England, chronic pulmonary disease as a cause of death ranks in frequency with rheumatic, hypertensive and ischemic heart disease, not because of a specific industrial hazard, but because of a common factor, exposure to a humid, highly polluted atmosphere. Chronic cor pulmonale and chronic obstructive emphysema are much more common in men than in women. Flint[2] studied 300 patients admitted with congestive heart failure to Sheffield City Hospital in one year (1952–1953) and found that the cause of the heart failure in 40 per cent of the males and 8.5 per cent of the females was chronic cor pulmonale, usually due to chronic obstructive emphysema.

Improved treatment of pulmonary infections and increasing thoracic surgery indicate a future rise in the incidence of chronic pulmonary insufficiency and chronic cor pulmonale.

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I. RESPIRATORY INSUFFICIENCY

A. *Physiology of Respiratory Insufficiency*

The primary function of the lung is the addition of oxygen and the removal of carbon dioxide from blood. The chest wall, its musculature and the diaphragm function as a bellows which communicates with the outside environment via an airway. Gaseous exchange occurs in the alveoli which fill the bellows. In order for this system to function properly: (1) the airway must remain patent, (2) the bellows must be able to function normally, (3) inspired air must mix with the air present in the alveoli, (4) blood must be evenly distributed to the various alveolar capillaries, (5) there must be an adequate amount of alveolar surface in contact with normally perfused capillaries and (6) there must be no impedance to diffusion of oxygen across the alveolar capillary membrane.

The major phases of lung function may be categorized as follows: (1) the *ventilation* function or the mass exchange of air between the lungs and the atmosphere, (2) the *distribution* function (intrapulmonary mixing) which deals with the distribution of inspired air to the alveoli, (3) the distribution of mixed venous blood to the alveolar capillaries or *capillary per-*

fusion and (4) the interface *diffusion* function which deals with the molecular exchange of gas across the semipermeable alveolar capillary membrane. The *cleansing* function of the lung which deals with the disposal of foreign material will be discussed separately from ventilation for purposes of emphasis. The *circulation* of the lung, exclusive of the distribution of venous blood to the capillaries, will be discussed in section II.

These phases of pulmonary function have been arbitrarily defined and represent only a small number of the known functions of the lungs. For example, the lung is richly supplied with sensory nerve endings which, in addition to their role in regulation of respiration, may be important in the control of the circulation. The greatly distensible vascular bed of the lung acts as a variable reservoir of blood which may, for example, temporarily protect against overload of the left ventricle. The respiratory bellows acts as a pump to aid venous return to the heart. The filtering function of the lungs is an important protective mechanism. By trapping white blood cells, the lungs may, under certain circumstances, help regulate the number of white cells in the peripheral blood.[3]

1. *Cleansing*

Cleansing is effected by external and internal disposal of foreign material. Endogenous inflammatory exudate and inhaled foreign substances become mixed with the mucus, which coats the tracheobronchial mucosa, and are constantly wafted toward the pharynx by ciliary action. Peristaltic action in the smaller bronchi, especially during forced respiration, probably also assists in this orad motion. Ciliary function may break down when the secretion is voluminous, is excessively viscid, or contains noxious substances (such as bacterial toxins). Chronic bronchial inflammation may result in permanent destruction of the cilia, often associated with squamous metaplasia of the epithelium. Under these circumstances, cough becomes important in keeping the airways clear. Once the injurious substance has reached the alveoli, an additional method of cleansing occurs: phagocytosis by macrophages.

In order for cough to clear bronchial secretion, the bronchus must not be continually occluded; air must be able to pass behind the secretion, at least, during the full inspiration which precedes cough. By using the intrinsic and accessory muscles of expiration against a closed glottis, the patient builds up a high intrabronchial pressure. The glottis is then opened suddenly, permitting a rapid flow of air to the outside. A pressure gradient is created which moves secretion toward the pharynx. The cough force will depend on the volume (mass) of air behind the obstruction and its acceleration produced by the sudden opening of the glottis.

Cough becomes ineffective with loss of expiratory force, such as occurs with asthenia or neuromuscular disorders. Cough effectiveness is reduced by a decreased vital capacity because the volume of air escaping after opening the glottis becomes too small to move secretion. Local restriction of pulmonary ventilation, due either to pleural or pulmonary fibrosis or to chest-wall deformity, results in regional impairment of the effectiveness of cough as a cleansing mechanism. Thus, such areas may be especially susceptible to secondary infection.

2. *Ventilation*

(A) *Normal Ventilation.* Normal ventilatory function requires maintenance of a patent airway, normal elasticity (compliance) of the lungs and an intact thoracic bellows. The latter includes the spine, rib cage and cartilages, the sternum, the intrinsic and extrinsic respiratory muscles, the pleura and the skin.

The *actual ventilation* for any given level of oxygen uptake depends on the stimulus to respiration,[4] determined by an aggregrate of many controlling factors. There are (1) chemical stimuli mediated directly through the respiratory center in the medulla or by way of the aortic and carotid bodies and possibly other chemoreceptors, (2) proprioceptive stimuli coming from the lungs themselves and from the musculoskeletal system and (3) controls from the higher centers of the brain as well as other nervous influences.

There are well-defined limits of normal ventilation for a given level of oxygen uptake. An excess of ventilation for a given oxygen uptake is referred to as *hyperventilation*, a de-

ficiency as *hypoventilation*. The best gage of maximum ventilatory capacity is the maximum breathing capacity test. This is the volume of air which can be breathed per unit of time (liters per minute) by means of maximum voluntary hyperventilation. The best measure of the reserve of ventilatory function present in any given metabolic state is the relation between the actual ventilation and the maximum breathing capacity.

The air present in the airways (mouth, nose, pharynx, larynx, trachea and bronchi down to the respiratory bronchiole) at the end of the inspiration does not take part in gaseous exchange. The volume of these passages is known as the *anatomic dead space*. Air enters the alveoli, partly by mass movement into alveoli which dilate during inspiration and partly by boundary diffusion between gas in the alveoli and the respiratory bronchioles. In the normal person at rest, all alveoli are not equally ventilated; some receive more and others less than their share of inspired air.[5] As a result, the dead space measured by physiologic technics is larger than the anatomic dead space (see below). The total volume of the inspired air which does not take part in gaseous exchange is known as the *physiologic dead space*.[6, 7] Fowler[6] has recently shown that the physiologic dead space is not constant. It averages about 150 ml. for young men and about 100 ml. for young women but varies with position, tidal volume, state of lung inflation, exercise and age; as a rule, it does not exceed 250 ml.

It is important to think in terms of *alveolar ventilation* rather than *total ventilation*, since with different breathing patterns the alveolar ventilation may vary considerably with the same total ventilation. A number of indirect technics have been used to measure the alveolar ventilation, but it can be quite adequately estimated for clinical purposes by assuming a dead space on the basis of the mean figures given above. For example, in a male with a total ventilation of 12 liters per minute at a rate of 20 respirations per minute, the tidal volume (T.V., fig. 1) will be 600 ml. Assuming the dead space to be 150 ml., the dead space ventilation will be 3 liters per minute and the effective alveolar ventilation will be 9 liters per minute.

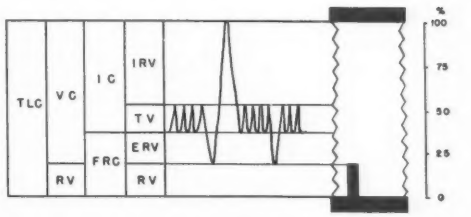

FIG. 1. The normal lung volumes and capacities. The *volumes* do not overlap and are primary. The *capacities* are made up of two or more volumes. I.R.V., inspiratory reserve volume; T.V., tidal volume; E.R.V., expiratory reserve volume; R.V., residual volume; T.L.C., total lung capacity; V.C., vital capacity; I.C., inspiratory capacity; F.R.C., functional residual capacity. Note, in the normal spirographic tracing, the vital capacity is an almost vertical straight line.

If, in this patient, the rate is changed to 30 per minute, but the total ventilation remains unchanged, the tidal volume would become 400 ml. Since the dead space remains fairly constant, the effective alveolar ventilation will fall to 7.5 liters per minute. It has been demonstrated that some alveolar ventilation occurs even when the tidal volume is less than the dead space.[7] This is so, partly because some centrally located alveoli have less dead space than peripheral ones and partly because inhaled gas moves as a spike with resultant diffusion between the gas in the alveoli and in the bronchioles.

The determination of lung volumes is often very helpful in assessing the functional effects of abnormalities of the lungs and the thoracic bellows. The various compartments of lung volume, as recently defined,[8] can be related to the schema of the respiratory system (fig. 1). A stop has been placed in the bottom of the bellows so that it cannot be completely emptied. The air remaining in the bellows when it has been maximally compressed represents the *residual lung volume* (R. V.), or the amount of air remaining in the lungs at the end of a maximal expiration. When the bellows is fully extended, the air it contains represents the *total lung capacity* (T. L. C.). The *vital capacity* (V. C.) is the volume of air which can be exhaled after a full inspiration; this is total lung capacity minus the residual lung volume. When

the force extending the bellows is removed and the bellows is allowed to find the point at which its retractile force is in balance with the factors tending to resist deformity, it will be at the *resting expiratory position* and the volume of air then in the lungs will represent the *functional residual capacity* (F. R. C.). The volume of air which can be exhaled starting at the expiratory end position is known as the *expiratory reserve volume* (E. R. V.). The *functional residual capacity* is the sum of the residual volume and expiratory reserve volume. The vital capacity minus the expiratory reserve volume is the *inspiratory capacity* (I. C.) or the volume of air which can be inhaled starting at the resting expiratory position. The residual volume and therefore the functional residual capacity and total lung capacity must be measured by indirect technics. All other compartments can be measured by simple spirometry.[7, 9a, 10, 11]

(B) *Abnormal Ventilation.* Abnormalities of ventilation may be divided into obstructive and restrictive ventilatory dysfunction. Restrictive ventilatory dysfunction is caused by disordered action of the thoracic bellows or diminished pulmonary distensibility. Obstructive ventilatory dysfunction is caused by narrowing of the air passages. It is apparent that an obstruction of a given size will have a much greater effect on air movement in the smaller airways than in the larger.

(1) *Obstructive ventilatory dysfunction:* The pathologic process resulting in airway obstruction may occur in the lumen of the bronchus, in the mucosa, in the wall of the bronchus or extramurally. The commonest pathologic process located in the lumen is tenacious secretion, the result usually of infection. Foreign bodies and neoplastic or inflammatory projections into the lumen are occasionally seen. The mucosa may be thickened and encroach on the lumen as a result of edema or congestion. Muscular spasm or inflammatory thickening of the bronchiolar wall narrows the lumen. The bronchus may be compressed extramurally by pathologic processes in the lymphatics such as lymphangitic carcinomatosis or by fibrosing processes in the pulmonary interstitium. Recent studies[12] have shown that loss of pulmonary elasticity, that is, loss of the power of the lung to retract after stretching, may also result in bronchial obstruction. The mechanism is that in order for air to leave the alveoli and enter the respiratory bronchiole during expiration, intra-alveolar pressure must become greater than intrabronchiolar pressure. Intra-alveolar pressure is exerted radially and tends to collapse the thin-walled respiratory bronchiole. This tendency toward collapse is normally resisted by the elastic retractile force of the lung. When the retractile force is decreased, bronchiolar collapse results. Since bronchiolar obstruction is associated with an increase in pressure gradient, bronchiolar collapse occurs much more readily in the presence of bronchiolar obstruction.

Airway obstruction results in an increased resistance to air flow which is manifested by a prolongation of the time necessary for expiration, as shown by the vital capacity breath in fig. 2.[12] The volume of the vital capacity may be normal or reduced, depending on the severity of airway obstruction, but the maximum breathing capacity is always reduced and is proportionally much smaller than the vital capacity. The work of breathing is increased.[13]

Airway obstruction is always more marked during expiration than during inspiration because of the normal narrowing and shortening of the bronchi which occurs during expiration and because of the mechanism of bronchiolar collapse (described above). This results in the phenomenon of air trapping; since air can get

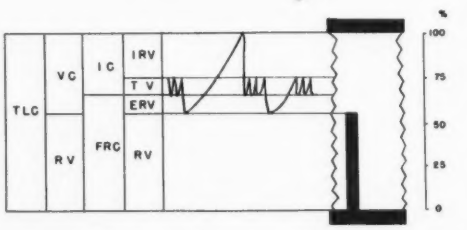

FIG. 2. The lung volumes and capacities in obstructive ventilatory dysfunction. The residual volume (R.V.) and functional residual capacity (F.R.C.) are greatly increased, although the total lung capacity is normal. The vital capacity (V.C.) and expiratory reserve volume (E.R.V.) are decreased. Note the marked delay in the performance time of the vital capacity.

into the lungs more readily than it can get out, the lungs become hyperinflated or emphysematous. The airway obstruction and hyperinflation may occur acutely and be reversible as in asthma[14] or may be chronic and irreversible as in chronic, diffuse obstructive emphysema.[15] The hyperinflation is demonstrated by an increase in the residual volume and functional residual capacity and by reduction in the vital capacity in relation to the total lung capacity (fig. 2).[9c] Lung cysts or bullae which communicate poorly with the airways may not be included in the measured residual lung volume.

(2) *Restrictive ventilatory dysfunction:* This may be defined as impairment of the ability to move air into and out of the lungs as a result of a defect in the thoracic bellows or diminished pulmonary distensibility. The lung bellows is a very complex mechanism and a great many different pathologic conditions may affect its function. Bellows action is disturbed by impaired function of the respiratory muscles in poliomyelitis, myasthenia gravis or diaphragmatic paralysis. Less directly, it may be impaired by asthenia or by pain associated with pleurisy or with abdominal or thoracic surgery. The function of the bellows is impaired, if the mobility of its walls is impaired. This can result from loss of mobility of the bony framework, such as ankylosis of the costovertebral articulations in ankylosing spondylitis, or increased rigidity of the costal cartilages with advancing age. Loss of mobility and loss of volume of the bellows occur in kyphoscoliosis and after thoracoplasty. Thickening of the skin as in scleroderma or burn cicatrix and thickening of the pleura, as in pleural fibrosis, can decrease bellows mobility. Finally, all of the structures of the thoracic bellows may be intact but the distensibility of the lung may be reduced. This results from diffuse pulmonary fibrosis or congestion, or a process in the pleural space, such as pleural effusion or pneumothorax.[9b, 16-18]

The position and mobility of the various structures of the thoracic bellows are the result of a balance of opposing forces so that loss of function of a portion of the bellows can often be partially compensated. When an artificial pneumothorax is induced, it can be shown that the volume of the lung decreases on the treated side, but the girth of that hemithorax increases. Similarly, an increase in excursion of the diaphragm follows restriction of the chest wall with a tight bandage.

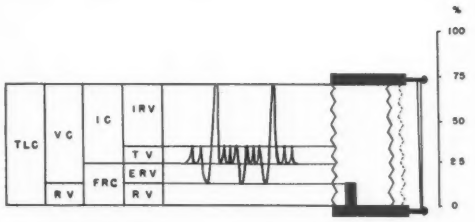

FIG. 3. The lung volumes and capacities in restrictive ventilatory dysfunction. The total lung capacity (T.L.C.) is decreased. The bellows is depicted as being reduced in volume and as being restricted in distensibility. The functional residual capacity (F.R.C.), residual volume (R.V.) and vital capacity (V.C.) are reduced. There is no delay in performance of the vital capacity.

Lung volume studies in restrictive ventilatory dysfunction show that the total lung capacity is reduced. The vital capacity is usually decreased proportionally to the reduction in total lung capacity, but the residual volume and functional residual capacity are either reduced or remain normal (fig. 3).

Restrictive ventilatory dysfunction often produces little pulmonary disability providing the airways remain patent. Although the stroke volume of the bellows or the vital capacity is reduced, in the absence of increased resistance to air flow, the patient can breathe with virtually all of the stroke volume at a more rapid respiratory rate. The maximum breathing capacity is thus proportionally much larger than the vital capacity.

(3) *Combined ventilatory dysfunction:* Restrictive ventilatory defects are often accompanied by an impairment of cleansing function; consequently, these patients show increased susceptibility to lower respiratory tract infection and, therefore, develop airway obstruction superimposed on the restrictive defect. This may be acute and transient, or may eventuate in the permanent structural changes of diffuse obstructive emphysema. Patients with combined restrictive and obstructive ventilatory dysfunction show a delay in emptying of the lungs during the vital capacity

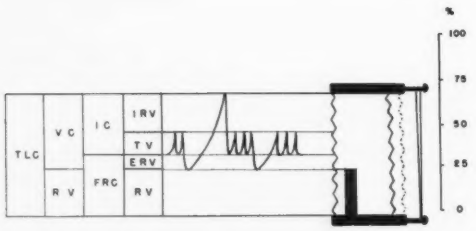

FIG. 4. The lung volumes and capacities in combined restrictive and obstructive ventilatory dysfunction. The total lung capacity (T.L.C.) is decreased. The residual volume (R.V.) and functional residual capacity (F.R.C.) are large, both in relation to the total lung capacity (T.L.C.) and in absolute terms. There is marked delay in the performance of the vital capacity.

maneuver. Their total lung capacity is decreased and the residual volume and functional residual capacity are increased (fig. 4). Their maximum breathing capacity is proportional to the vital capacity or may even be proportionally smaller than the vital capacity.

3. *Distribution*

The normal occurrence of slight degrees of inequality of alveolar ventilation has already been noted above. However, uneven alveolar ventilation of more marked degree may lead to pulmonary insufficiency, even though the minute volume of breathing and the total alveolar ventilation are normal.[5, 19, 20] Regional underventilation may be the result of bronchiolar obstruction or total loss of distensibility. Consider a situation where pulmonary capillary perfusion is uniform and alveolar ventilation is essentially even throughout the lung, except for one area where there is underventilation (fig. 5*B*). In the alveoli in this area, the partial pressure of carbon dioxide will be high and of oxygen, low. Consequently, the blood leaving this area will contain excess carbon dioxide and be undersaturated with oxygen. The excess carbon dioxide in the mixed arterial blood will stimulate the respiratory center resulting in an increase in total ventilation (fig. 5*C*). There will be a fall in carbon dioxide tension and a rise in oxygen tension in the normal alveoli which are being hyperventilated. The diffusibility of carbon dioxide is high and, therefore, the carbon dioxide tension will be low in the alveoli leaving these capillaries. Oxygen is much less diffusible than carbon dioxide and the shape of the dissociation curve of hemoglobin for oxygen is such that, in the range above 90 per cent, a considerable rise in partial pressure of oxygen results in only a very small rise in saturation of hemoglobin. Consequently, hyperventilation of normal alveoli cannot result in a marked increase in arterial oxygen saturation of the blood leaving their capillaries. The net effect of hyperventilation in this circumstance will be to correct the hypercapnia but not the hypoxemia. If the underventilation of alveoli is widespread, or if the impairment of ventilatory function is so great that the patient cannot hyperventilate adequately, hypoxemia will be associated with hypercapnia. This is the commonest mechanism of hypoxemia in pulmonary disease.

Figure 5*F* demonstrates a situation in which alveolar capillary perfusion and ventilation are uniform throughout except for a group of alveoli which are hyperventilated. The arterial blood leaving this latter area will have a slightly higher saturation with oxygen, and will contain less carbon dioxide than the blood from the rest of the lung. There will be little alteration of mixed arterial blood and the effect will be to increase the physiologic dead space.

4. *Capillary Perfusion*

Inequalities of perfusion also may have a profound effect on the results of uneven alveolar ventilation. Underperfusion of normally ventilated alveoli will have the same effect as hyperventilation of normally perfused alveoli, that is, the physiologic dead space will be decreased (fig. 5*E*). This occurs in areas of pulmonary embolization and in primary pulmonary hypertension. In the case of hypoventilation of alveoli, if the alveolar capillaries are also underperfused (fig. 5*D*) the effect of underventilation on the arterial blood gases will tend to be nullified.[21] Reduction of blood flow through underventilated portions of the lung occurs very frequently in extensive chronic pulmonary disease. The mechanism of local decrease in capillary blood flow in such instances is due to many factors which will be discussed in detail in section II. In some cases, there is an

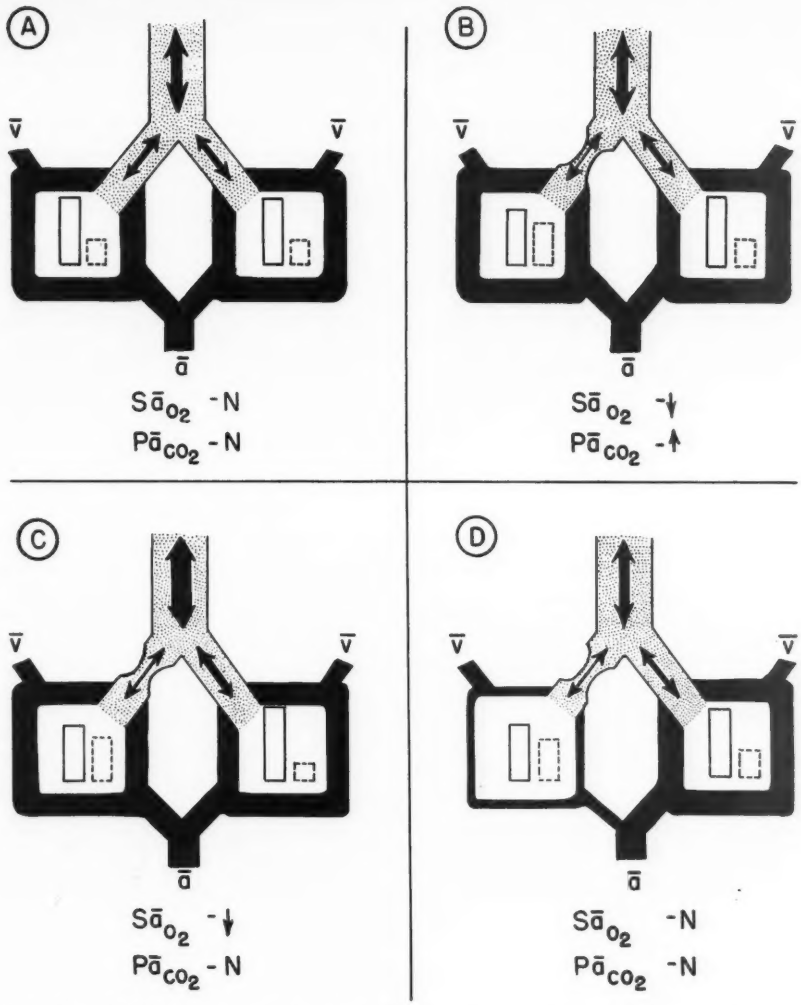

FIG. 5. (Part 1) Schema of normal and abnormal states of alveoli. The following symbols are used: the stippled area in the bronchioles represents the respiratory dead space, the thickness of the vertical arrow in the bronchiole represents total ventilation; the thickness of the two smaller arrows represents alveolar ventilation; the solid black represents the alveolar capillary with mixed venous blood ($\bar{v}$) entering at the top and mixed arterial blood ($\bar{a}$) leaving at the bottom; the solid rectangle represents alveolar partial pressure of oxygen and the dotted rectangle alveolar partial pressure of carbon dioxide; $S\bar{a}_{O_2}$ represents saturation of arterial blood with oxygen; $P\bar{a}_{CO_2}$ partial pressure of carbon dioxide in arterial blood. N., normal; ↓, decreased; ↑, increased.

A. Schema of two normal alveoli with their bronchioles.

B. Regional hyperventilation due to airway obstruction. Regional bronchiolar obstruction is depicted by narrowing of the air passage to one alveolus. This results in reduced alveolar ventilation, with an increase in alveolar P_{CO_2} and decrease in alveolar P_{O_2}. There is a consequent reduction in $S\bar{a}_{O_2}$ and increase in $P\bar{a}_{CO_2}$. The increased $P\bar{a}_{CO_2}$ may cause hyperventilation which is shown in *C*.

C. Regional bronchiolar obstruction with compensatory hyperventilation. The hyperventilation decreases P_{CO_2} and increases P_{O_2} in the normal alveoli with resultant elimination of excess CO_2 from arterial blood. Hyperventilation cannot compensate for the decreased $S\bar{a}_{O_2}$ of the blood coming from the hypoventilated alveoli and $S\bar{a}_{O_2}$ remains low.

D. Reduced capillary perfusion with regional hypoventilation. There is a decrease in blood flow through the capillary of the hypoventilated alveolus and as a result the regional ventilation has no effect on mixed arterial blood.

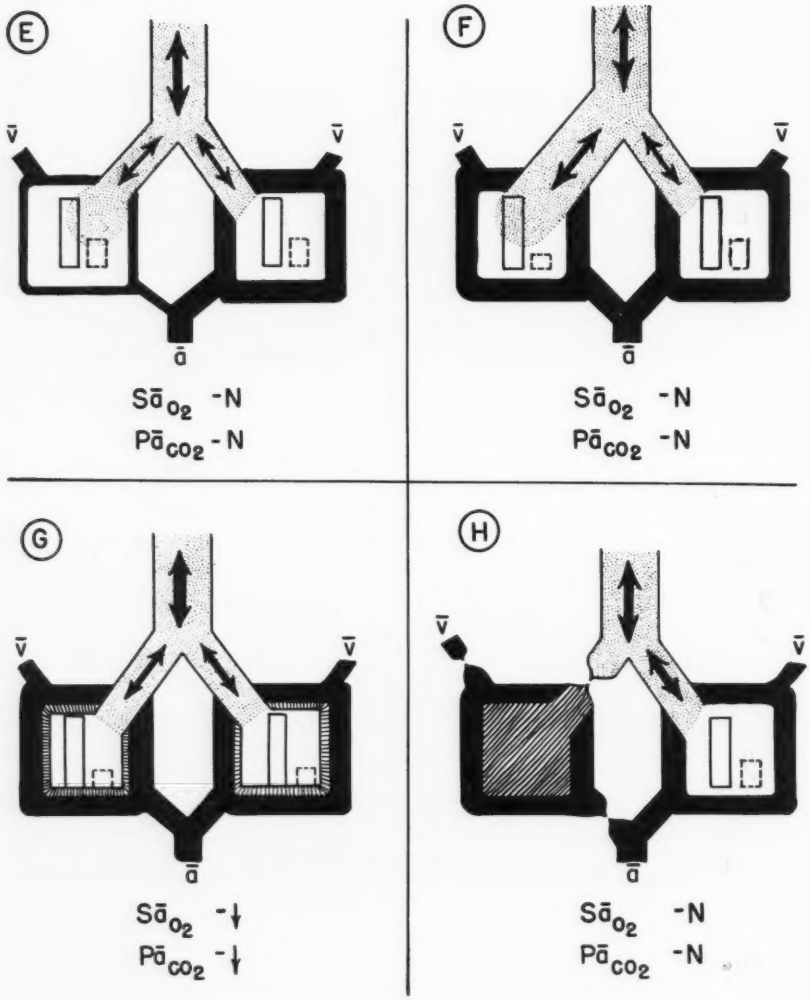

FIG. 5. (Continued)

E. Reduced capillary perfusion with normal ventilation. Alveolar ventilation is normal, but there is a regional decrease in capillary blood flow. The effect is to increase the respiratory dead space without effect on arterial blood gases.

F. Regional hyperventilation with normal capillary perfusion. Capillary blood flow is normal but there is regional hyperventilation of alveoli which results in increased respiratory dead space.

G. Decreased maximum diffusing capacity for oxygen due to alveolar-capillary block. This results in a marked depression of $S\bar{a}_{O_2}$. There is also hyperventilation which causes a fall in alveolar and arterial P_{CO_2}. The latter is possible because the diffusibility of CO_2 is so much greater than that of oxygen.

H. Decreased maximum diffusing capacity of the lung is due to loss of area of functioning alveolus in contact with functioning capillary.

actual anatomic obliteration of the vascular bed, due to fibrosis or destruction of capillaries as in emphysema; in many cases, the localized increased resistance to blood flow may be a result of local hypoxia. Expansion of anastomotic channels between the bronchial and the pulmonary arteries in this area may result in a more "arterialized" mixture of blood passing through these hypoventilated areas with less contamination of systemic arterial blood. In still other disease states decreased distensibility of the vessels may result in locally increased resistance to flow as in fibrosis, pneumothorax or pneumonia.

5. *Diffusion*

To enter the blood, gases must penetrate the alveolar epithelium, the interstitial space of the alveolar septum and the capillary endothelium. This movement occurs mainly by a process of diffusion or the movement of molecules from a region of higher to one of lower partial pressure. The diffusing capacity of the lungs is defined as the quantity of a gas, usually oxygen, transferred each minute per millimeter of mercury difference in partial pressure of the gas across the alveolar capillary barrier.

The diffusing capacity of the lungs is determined by the surface area available for diffusion and the thickness and character of the tissues constituting the alveolar barrier. The total surface for gas exchange consists of the area of functioning alveoli in contact with functioning capillaries. In man, this area is estimated to be about 90 square meters at rest. It is enlarged during exercise, probably as a result of an increase in the number and size of patent capillaries and in the number of functioning alveoli. It is reduced following pulmonary resection, with destructive pulmonary disease and in pulmonary fibrosis (fig. 5*H*). A reduced oxygen diffusing capacity also may occur in pulmonary emphysema because many capillaries are in contact with poorly ventilated alveoli.

Thickening of the alveolar capillary barrier by disease will impede the passage of the oxygen molecules into the capillary blood and so will decrease the oxygen diffusion capacity of the lung[19, 20, 22] (fig. 5*G*). Because of greater solubility, carbon dioxide is more than 20 times as diffusible as oxygen and is much less affected by thickening of the alveolar capillary membrane. Consequently, where the main abnormality is thickening of this membrane, severe degrees of hypoxemia may coexist with normal partial pressures of carbon dioxide in arterial blood. Indeed, the partial pressure of carbon dioxide in arterial blood may be low as a result of the associated marked hyperventilation usually seen in this condition.[9b]

This thickening of the alveolar capillary membrane may occur as a result of intra-alveolar or interstitial pulmonary edema or it may be due to granulomatous or neoplastic infiltration. The term "alveolar capillary block" has been applied to conditions in which the chief disturbance in pulmonary function is a decrease in the diffusing capacity.[22] In these cases there is usually restrictive ventilatory dysfunction, little or no reduction of maximum breathing capacity and no abnormality of distribution of inspired air. This has been found to occur at times in beryllium granulomatosis, certain types of diffuse pulmonary sarcoidosis, pulmonary scleroderma, asbestosis and diffuse pulmonary endolymphatic carcinomatosis.

B. *Relation of Function to Pathology*

Many pathologic conditions affect the lung and produce functional disturbances. The same abnormal physiologic change may result from different pathologic conditions and a particular disease may give rise to many functional patterns. This discussion will, therefore, be confined to the relationships between the pathologic processes and derangement of function in interstitial pulmonary infiltration, or "pulmonary fibrosis," and chronic diffuse obstructive emphysema.

The word "fibrosis" has been used in various ways by different observers. It has become a general term for a large number of conditions, in which the only common factor is the proliferation of connective tissue. For want of a better term, the word has persisted in the literature and in the day to day discussion of patients with pulmonary disease. However, the term is inaccurate, since the pathologic process in many conditions may be granulomatous or even neoplastic. Better perhaps would be "interstitial

pulmonary infiltration," which may then be qualified as to etiology, as to extent, and as to whether the process is predominantly fibrous or granulomatous. When the process is localized or focal, there are no demonstrable effects on cardiopulmonary function. The effect of diffuse disease depends to a large extent on the location of the disease with respect to the various functional elements of the lung.[9b, 17, 22] If the process is localized in the alveolar septa, it may result in alveolar capillary block with marked hypoxemia or may give rise to constriction of the vascular bed of the lung with resultant pulmonary hypertension. Chronic diffuse obstructive emphysema may result when there is loss of pulmonary elasticity and bronchiolar obstruction. When the process is located primarily in alveolar spaces and results in loss of both alveolar ventilation and capillary perfusion, little loss of function results unless the process is very extensive.

Chronic diffuse obstructive emphysema may be defined as a syndrome in which there is hyperinflation of the lungs associated with diffuse obstruction of the small airways and loss of pulmonary elasticity.

The process may be secondary to diffuse interstitial infiltration or may be of the type called idiopathic. While all agree that diffuse airway obstruction and loss of pulmonary elasticity are outstanding, there has been much controversy as to which of these processes is primary. The resolution of the problem is a difficult one since loss of pulmonary elasticity causes bronchiolar collapse during expiration. Certainly, in most cases it would appear that chronic bronchial infection with obstruction has been important in the genesis of the disease.[15] However, there are occasional patients who are asymptomatic until an episode of lower respiratory tract infection makes evident the presence of diffuse obstructive emphysema. It is possible that in these patients a primary degenerative process has caused loss of pulmonary elasticity and bronchiolar obstruction. Some credence is lent to this theory by recent pathologic studies which have demonstrated almost complete obliteration of the intrapulmonary bronchial arteries.[23]

Chronic diffuse obstructive emphysema is associated with an absolute increase in the residual volume and functional residual capacity and a decrease in the vital capacity and the maximum breathing capacity. There is a marked increase in the work of breathing.[13] The increase in the functional residual capacity coupled with the widespread but irregular loss of pulmonary elasticity and bronchiolar obstruction results in a marked impairment of the distribution of inspired air. Under certain circumstances, obliteration of pulmonary capillaries is a feature and this, in association with a patchy increase in intra-alveolar pressure, results in inequality of capillary blood flow. In the earliest phases, impaired distribution is slight and the chief abnormality is the disturbed mechanics of ventilation. As the disease progresses, hyperventilation may result in a decrease of the partial pressure of carbon dioxide in arterial blood during exercise without significant hypoxemia. At a later stage, particularly when there is superimposed infection, hypoxemia occurs. Later, hyperventilation becomes inadequate and hypercapnia results. Finally, the respiratory center becomes relatively insensitive to carbon dioxide and hypoventilation results. Under these circumstances the chief stimulus to respiration is hypoxemia acting on the aortic and carotid chemoreceptors.[9c, 24]

C. *Diagnosis of Respiratory Insufficiency*

1. *Clinical Examination*

The diagnosis of respiratory insufficiency generally requires an evaluation of dyspnea, since this is the commonest presenting symptom. Primary cardiac disease with secondary pulmonary congestion must be excluded. The history is of considerable help. Wheezing or a conscious difficulty in moving air indicates the presence of airway obstruction. Sighing respiration, hyperventilation at rest without associated effort dyspnea or gross inconstancy of the amount of effort causing dyspnea suggest a psychogenic origin of symptoms. The presence of chronic cough, often considered minor by the patient, and a history of recurrent lower respiratory tract infection point to respiratory insufficiency as a possible cause of dyspnea.

The physical examination is of value, chiefly in detecting the gross evidences of pulmonary disease. Inspection quickly discloses the presence of a thoracic deformity. The increase in anteroposterior diameter of the chest may be misleading. While it is often a prominent feature of chronic obstructive emphysema, it may also be present in simple overdistension of the lung as in senile emphysema, where there is very little functional impairment. An increased anteroposterior diameter may be absent in chronic diffuse obstructive emphysema associated with diffuse interstitial infiltration in which there has been a decrease of total lung capacity. Far more important is the frequent fixation of the chest near the position of inspiration with marked limitation of chest wall excursion. Diaphragmatic excursions as determined by percussion are decreased. Frequently one may see paradoxic outward bulging of the upper abdominal wall during expiration. Prolongation of the expiratory time, beyond the normal four seconds, during determination of vital capacity can be readily detected at the bedside. The intensity of the breath sounds on auscultation does not correlate well with the degree of ventilatory dysfunction. Rales serve only to indicate the presence of pulmonary disease without indicating functional significance. The importance of the elicitation of rhonchi or the localized wheeze cannot be overemphasized. These should be listened for during both quiet and forced expiration. Frequently, a wheeze can be detected only by listening to the dependent lung with the patient in the lateral recumbent position. Bronchospirometric studies have shown that when the patient is in the lateral recumbent position the dependent lung carries out more of the total ventilation than when the patient is upright.[25]

2. *Roentgenologic Examination*

The single full inspiration chest roentgenogram may be misleading from the functional standpoint. Such a film serves to indicate the presence of pulmonary disease but gives no good indication as to the presence or extent of disturbed pulmonary function. Severe disturbances of pulmonary function may be present with little change in the roentgenogram. Extensive disease processes with much structural changes may heal without giving rise to any roentgenologic residual.[17] Furthermore, abnormalities in bronchial function are not manifest in the roentgenogram.

Much more information is obtained by a careful fluoroscopy of the lungs oriented toward functional evaluation. The skilled observer can often make a remarkably accurate estimate of the type and degree of ventilatory dysfunction by this means. The degree of filling and emptying of the lungs can be estimated by changes in volume and density of the lungs. Airway patency can be judged from the rate of emptying. Localized inequalities of ventilation due to bronchial narrowing or loss of elasticity can be detected by trapping of air in these areas during forced expiration. Chest wall and especially diaphragmatic motion can be evaluated. Shift of the mediastinum from the midline during respiration indicates inequalities in emptying or filling of the two lungs. Chest roentgenograms taken in the frontal projection in both full inspiration and full expiration are better than the single inspiration roentgenogram but are no substitute for fluoroscopy.

3. *Pulmonary Function Studies*

A complete physiologic evaluation is impossible without pulmonary function studies. The technics of pulmonary function testing have been amply reviewed recently and will be dealt with only briefly here.[7, 9a, 10, 11, 17, 26, 27] Ventilatory function can be evaluated by means of determination of lung volumes, tidal volume and minute ventilation during rest and exercise, and maximum breathing capacity. Alveolar ventilation can be calculated on the basis of an assumed physiologic dead space. Reversible airway obstruction can be studied by determining the effect of a bronchodilator drug on the maximum breathing capacity,[14] or on one of the tests which relate the vital capacity to time. The distribution of inspired gas can be evaluated during measurement of the functional residual capacity[9a] or by one of the single breath tests using rapid electronic analyzers.[7] The maximum diffusing capacity of the lung requires more elaborate analytic technics, but its impairment can often be inferred if there is

arterial hypoxia without significant dysfunction of ventilation or distribution.[19, 20] Much information can be obtained by study of arterial oxygen saturation while the patient is breathing room air and while breathing oxygen. The determination of partial pressure of carbon dioxide, by calculation from the determined carbon dioxide content and pH of the blood, is of great value for diagnosis and for following the course of patients.

Pulmonary function tests attain their greatest usefulness when carefully evaluated in conjunction with clinical and roentgenologic studies. Pathologic processes may be quite extensive and yet be accompanied by little or no abnormality of pulmonary function tests. Loss of function following disease must be quite large for the test to be outside the wide range of normal. Function tests, furthermore, do not make a pathologic or etiologic diagnosis.[17] Accordingly, we have found it helpful in planning and evaluating therapy to record a physiologic as well as a pathologic and etiologic diagnosis. This is similar to the practice introduced some years ago for heart disease by the New York Heart Association and adopted by the American Heart Association.

II. Chronic Cor Pulmonale

A. *General Considerations*

Chronic cor pulmonale may be defined as right ventricular hypertrophy resulting from disease involving the lung and the pulmonary circulation. Right ventricular failure need not be present. Excluded from this category are other causes of right ventricular hypertrophy such as mitral stenosis, congenital heart disease and left ventricular failure.

Only in recent years is the true incidence of chronic cor pulmonale being recognized.[1, 2] In the past, cases were overlooked not only in clinical studies but also at necropsy. The cachexia of chronic pulmonary disease is often associated with some degree of atrophy of the entire heart, so that relative hypertrophy of the right ventricle may be overlooked. With the employment of technics, in which a ratio of left to right ventricular weight or left ventricular and septum to right ventricular weight is obtained, a higher necropsy incidence of chronic cor pulmonale is already being reported.[28-30]

B. *Causes of Chronic Cor Pulmonale*

From the definition given of chronic cor pulmonale it is obvious that the primary cause is usually some form of pulmonary disease. However, the involvement of the lungs must be bilateral and diffuse, and not unilateral or focal. In the past, chronic cor pulmonale has usually been classified on the basis of the anatomic location of the pulmonary disease which causes it.[31, 32] A more useful classification correlates anatomic and functional abnormalities and, in addition, has important therapeutic implications. It divides the causes of chronic cor pulmonale into two main categories: Type I, pulmonary diseases associated with chronic diffuse obstructive emphysema and type II, pulmonary diseases in which the pathologic process is localized in or about the pulmonary vessels. These two types are not rigidly exclusive.

1. *Type I: Pulmonary Disease with Predominant Chronic Diffuse Obstructive Emphysema*

Chronic diffuse obstructive emphysema is the commonest cause of chronic cor pulmonale in the United States. Therapy tends to be much more satisfactory in this group than in chronic cor pulmonale, due to disease mainly localized in or about the pulmonary vessels. In the former condition intensive treatment of infection produces an adequate airway, improves alveolar ventilation, enlarges the pulmonary vascular bed and abolishes hypoxia, thus reversing the very changes which caused the chronic cor pulmonale.

The commonest cause of chronic diffuse obstructive emphysema is chronic bronchitis, often, but not necessarily, associated with bronchiectasis.[9c] Chronic bronchitis is, therefore, the commonest cause of chronic cor pulmonale in this country.

Bronchial asthma produces chronic cor pulmonale only if it is severe, of long standing and associated with a secondary infectious bronchitis. Excluded from this discussion is the acute transitory elevation of pulmonary artery

pressure observed during an acute prolonged episode of bronchial asthma (status asthmaticus).

Kyphoscoliosis, when of more than moderate severity, frequently leads to chronic cor pulmonale. In kyphoscoliosis, respiratory embarrassment and eventually cardiac dysfunction are usually not present early in life but develop only after the passage of time. This time interval is an important clue to the pathogenesis of the pulmonary and circulatory changes. During this interval, these patients suffer from acute recurrent and chronic bronchopulmonary infections because of interference with bronchial cleansing, impairment of the bellows action of the chest wall and diaphragm and because of a poor tussive mechanism. These eventuate in the development of chronic obstructive emphysema. We have not seen chronic cor pulmonale in such patients in the absence of these changes. There is no evidence that kinking of the main pulmonary artery is important in this regard.

Tuberculosis is not an infrequent cause of chronic cor pulmonale. In most instances, the tuberculosis has been of long standing and has resulted in severe chronic obstructive emphysema. Again, it is the bronchial factor which is important. Associated extensive loss of pulmonary parenchyma by necrosis with scarring, marked pleural reaction, extirpative surgery and collapse measures often play a secondary role.

Sarcoidosis causes chronic cor pulmonale only when the pulmonary involvement is diffuse. The roentgenographic appearance may be deceptive; usually the pulmonary involvement is more marked than is evident. Pulmonary sarcoidosis severe enough to cause chronic cor pulmonale may be of two types.[22, 23] In the first type, the granulomata are predominantly peribronchiolar and endobronchial in location, causing diffuse bronchiolar obstruction and severe obstructive emphysema. In the second type, the granulomata are located predominantly interstitially and in the interalveolar septa, compressing arterioles and capillaries. If the changes of this latter type predominate, this group will fall into the type II category of causes of chronic cor pulmonale. A patient however may have varying combinations of both types.

2. *Type II: Pulmonary Disease with Predominant Involvement of Vessels*

This category of pulmonary disease leading to chronic cor pulmonale includes diseases with involvement predominantly of the pulmonary vessels (intraluminal or extraluminal). Among the intraluminal processes are multiple repeated small pulmonary emboli, the importance of which has only recently been fully recognized. The embolizations may take place over protracted periods of time, frequently without the usual clinical manifestations, and eventually lead to a marked reduction in the pulmonary vascular bed. The emboli are recognized only when lung sections are examined pathologically. With organization and recanalization, many of the vessels show changes that resemble arteriosclerosis, especially fibrous intimal thickening.[34] Such cases in the past have not infrequently been considered as examples of primary pulmonary hypertension. However, it seems quite certain now that primary pulmonary hypertension as an entity does exist. In this condition, there are progressive right heart enlargement and right heart failure, no signs of pulmonary disease at autopsy, but the advanced cases show extensive changes in the pulmonary arterioles and arteries. There is suggestive evidence that these sclerotic changes are secondary to some unknown factor causing an increase in pulmonary arterial pressure.[35] Sickle cell anemia with multiple small pulmonary capillary thromboses has also been described as causing chronic cor pulmonale.[36] Schistosomiasis, due to *Schistosoma mansoni* or *hematobium*, may cause an extensive obliterating endarteritis due to massive and repeated infections of the lung with the ova of the parasites. It is a rather common cause of chronic cor pulmonale in Egypt. The obliterating endarteritis is often followed by canalization of the occluding tissue by newly formed capillaries that sometimes dilate to form angiomatoid structures. These have been considered as typical of pulmonary schistosomiasis, and in some way an adaptation to the obstruction to the pulmonary circulation.[37]

Extraluminal processes include granulomatous or fibrous proliferation in the interstitial tissue of the lung, particularly in the interalveolar septa. These conditions, in addition to producing alveolar capillary block, also cause a marked reduction in the caliber of the pulmonary vascular bed, thus increasing greatly the resistance to blood flow. In this group may be placed beryllium granulomatosis, scleroderma, acute interstitial fibrosis of the lung (Hamman-Rich syndrome),[38] silicosis, sarcoidosis, of the second type discussed above, and other diffuse pulmonary granulomatoses of undetermined etiology. Metastatic carcinomatosis of the lung, with perivascular lymphatic spread, may produce a carcinomatous endarteritis as well as mechanical compression of the arteries and arterioles by the desmoplastic character of the cords of carcinoma cells.[39] Extension of such endolymphatic carcinomatosis into the interalveolar septa may also produce alveolar capillary block to a varying degree. Further reduction of the pulmonary vascular bed may sometimes result from multiple emboli, composed of either tumor tissue or blood clot from deep vein thromboses in the lower extremities. The progression of events leading to right heart hypertrophy, dilatation and failure is often so rapid that this type has been called subacute cor pulmonale.[40] Marked compression of the main pulmonary artery or both of its major branches, while strictly speaking not pulmonary disease, has been reported to cause chronic cor pulmonale. This has been described with an aneurysm of the concave portion of the ascending aorta or due to carcinomatous lymph nodes. Massive thromboses in the main pulmonary arteries, usually secondary to emboli, but sometimes autochthonous, are also on record as a rare cause of chronic cor pulmonale.[41]

3. *Combinations of Types I and II*

Combinations of conditions in the above two categories may occur. The commonest combination arises from the complicating presence of chronic obstructive emphysema in conditions in which the pathology tends to be localized primarily about the pulmonary vessels, as in sarcoidosis (see above). In some cases of silicosis the predominantly perivascular location of the nodules was the main cause of the pulmonary hypertension and chronic cor pulmonale. However, in most cases of silicosis when severe respiratory insufficiency and chronic cor pulmonale occur, there is complicating severe diffuse obstructive emphysema.[28, 30, 33] The latter is chiefly responsible for the development of chronic cor pulmonale. In some silicotic patients, thrombosis of a major branch of the pulmonary artery occurs and contributes to the reduction in the pulmonary vascular bed.[30]

C. *Pathogenesis of Type I Chronic Cor Pulmonale*

The development of hypertrophy of the right ventricle in chronic diffuse obstructive emphysema is a result of right heart strain. The increased work of this chamber results from increased resistance to pulmonary blood flow and sometimes from augmented cardiac output. In considering particular pathologic processes in detail, it is important to note whether or not they are reversible, since it is this very element of reversibility which offers hope when therapy is attempted.

1. *Increased Resistance to Pulmonary Blood Flow*

Increased resistance to blood flow through the lungs in chronic obstructive emphysema results from: (A) a reduction in the cross-sectional diameter and distensibility of the pulmonary vascular bed, (B) increased viscosity of the blood if polycythemia has developed and (C) possibly certain dynamic consequences of an expansion of intrapulmonary vascular shunts.

(A) *Reduction in Cross-Sectional Diameter and Distensibility of the Pulmonary Vascular Bed.* Normally, the pulmonary circulation operates under low pressure with a low resistance to blood flow. This low resistance is a result of the large capacity and caliber of the vascular bed, and the marked distensibility of the pulmonary vessels.[42] In normal man in the upright position, pressure in the pulmonary artery remains unchanged even when the cardiac output is doubled.[43, 44] Brofman[45] was able to show in a patient with hyperthyroidism, that even with the right pulmonary artery occluded

by means of an inflatable balloon-tipped cardiac catheter and with a left lung flow of approximately eight times normal, only a moderate increase in pulmonary artery pressure resulted. He concluded that in the presence of a competent left ventricle, the left lung in man accommodates 8 to 10 times normal flow without increments in pressure or evidence of right ventricular failure. Thus, a marked increase in pulmonary blood flow may occur, with only an increase in velocity of flow and in the caliber of the vascular bed, but with little or no increase in pulmonary artery pressure. Contributing to the increase in size of the vascular bed is not only the distensibility of the individual vessels, but also the opening up of vessels formerly not functioning for flow. The distensibility of the pulmonary vascular bed may be lowered by a reduction in the total number of vessels in the lung (since each vessel contributes its increment of distension), by a reduction in caliber of the vessels, and by conditions making the individual vessel walls more rigid.

The following pathologic changes contribute to the reduction in cross-sectional diameter and distensibility of the pulmonary vascular bed:

(1) Rupture of interalveolar septa, with the conversion of many small air spaces into fewer larger air spaces and bullae, results in a true loss of capillary bed. In addition, many of these bullae actually compress surrounding parenchyma and so collapse some of the remaining capillary bed. Treatment may reduce the size of bullae.

(2) Further reduction in the vascular bed in the lung results from loss of pulmonary parenchyma in areas of necrosis with replacement by scar which is relatively avascular, and which frequently is supplied with blood from the bronchial rather than the pulmonary arteries.

(3) Vascular narrowing and diminished distensibility may result from a number of changes. Actual compression of vessels occurs in the scattered areas of alveolar exudate, atelectasis and entrapment of air; this is reversible. Cuffing of arterioles by inflammatory exudate and fibrosis will also produce narrowing. In many of the arterioles, capillaries, and sometimes small pulmonary arteries, actual thrombosis occurs. These changes may be partially reversible, the perivascular inflammation resolving without the development of scar tissue and the thrombotic vessels becoming recanalized. Vessel changes secondary to the development of increased intravascular pressure also contribute to vascular narrowing. These include endarteritis obliterans, medial hypertrophy, occasionally actual necrotizing arteriolitis, and not infrequently pulmonary atherosclerosis. These changes increase resistance to blood flow and hence pulmonary vascular pressure; the latter furthers the secondary hypertensive vascular morphologic changes. A vicious cycle thus may become established. It is obvious that the changes in the small vessels are more important than atheromatous changes in the pulmonary arteries unless the latter lead to actual thrombosis. It is known from studies of the lungs in other conditions where secondary vascular changes occur, such as mitral stenosis and some types of congenital heart disease associated with pulmonary hypertension, that many of the secondary vessel changes are reversible, particularly the endarteritis obliterans and the medial hypertrophy.

(4) Hypoxia is an important cause of vascular narrowing and increased pulmonary artery pressure.[46-50] Hypoxia produces an increase in pulmonary vascular resistance by an actual reduction in the caliber of the lung vessels, apparently by a direct action; the exact site of this vascular constriction is as yet unknown—various investigators have placed it in the pulmonary arterioles, capillaries or venules. Hypoxia may cause an increase in the residual blood in the lungs by a redistribution from the systemic circulation;[51] this would limit further increase in pulmonary vascular capacity. Hypoxia produces an increase in cardiac output; in the face of an already restricted pulmonary vascular bed, this contributes to the pulmonary hypertension. Hypoxia and its effects are reversible.

(B) *Polycythemia.* Secondary polycythemia when present is the result of direct hypoxic stimulation of the bone marrow. However, in spite of the presence of marked arterial oxygen

desaturation, many patients with chronic obstructive emphysema are not polycythemic. It has been suggested that chronic infection (bronchopulmonary) may be one of the factors causing failure of the hematopoietic response.[52]

Secondary polycythemia is associated with an increased blood viscosity and an increased blood volume. The increased viscosity increases the resistance to blood flow in the lungs, but to what extent is unknown.

The increased blood volume in secondary polycythemia is due almost entirely to an increase in red cell mass; the plasma volume is usually normal except in the presence of congestive failure, or immediately after recovery from failure. This hypervolemia is usually associated with an increased venous return, an increased cardiac output and probably an increased residual volume of blood in the lungs.[48] An increase in the residual blood in the lungs in the face of an already limited pulmonary vascular capacity may result in a further encroachment on the ability of the pulmonary vascular bed to accommodate an increased blood flow without an increase in pressure. Since satisfactory methods are not available for determining pulmonary residual blood volume, the importance of this factor cannot be evaluated.

Lewis and associates[53] have stressed that oxygen transport (product of cardiac output and arterial oxygen content) is frequently more important than cardiac output alone. Thus, secondary polycythemia in patients with chronic obstructive emphysema is an attempt at compensation, not only because the polycythemia may lead to an increased oxygen content of the arterial blood, but because the hypervolemia by increasing venous return to the heart helps to increase cardiac output and maintain a high pulmonary blood flow. Such indeed occurs in normal people exposed to high altitudes, where the adjustment to hypoxemia includes polycythemia, and often also increased cardiac output. However, in a patient with chronic obstructive emphysema, the deleterious effects of the polycythemia probably outweigh at some point the possible compensatory advantages, because the lungs have a vascular bed which is reduced in size and distensibility. It is possible that in the future the exact extent to which phlebotomy should be employed in therapy will be determined from correlative studies of viscosity, pulmonary vascular resistance, pulmonary residual blood, total blood volume and cardiac output. At present, we feel that phlebotomy should be utilized moderately in therapy, always in conjunction with all the other therapeutic procedures available to treat the pulmonary disease.

(C) *Intrapulmonary Vascular Shunts.* While there is not complete agreement about the extent or even the existence of precapillary anastomoses between the bronchial arteries and the pulmonary arteries in the *normal* human lung,[54, 55] their presence and considerable size has been clearly demonstrated in *diseased* lungs.[55] In dogs, following ligation of one pulmonary artery, collateral circulation from the bronchial arteries will expand to such an extent that one third of the cardiac output can be carried by the bronchial arteries on that side.

Large and numerous precapillary shunts between the bronchial and pulmonary arteries have been demonstrated in lungs with chronic bronchial infection, tuberculosis and chronic fibrosing disease. The expansion of these anastomoses in chronic obstructive emphysema has been related to their development or enlargement in granulation tissue, in areas of organizing pneumonitis, in the walls of bronchiectatic sacs and in areas of lymphoid hyperplasia and hypertrophied bronchial smooth muscle.

What could be the consequences of these functioning anastomoses between a high and low pressure system? (1) They might act to shunt desaturated pulmonary artery blood away from poorly ventilated areas of the lung in which they occur to the greatest extent; thus, whatever blood does pass through these poorly ventilated areas would have a higher oxygen content and less polution of the systemic blood would occur. (2) They increase the blood flow through the lungs and, in the presence of a restricted vascular bed, serve to elevate further pulmonary artery pressure (3) They tend to increase the work of the left ventricle, since in effect they are a shunt between the left ventricle and the left atrium. (4) They may produce an actual local reversal

of blood flow in the pulmonary artery towards the hilum in some areas[55]; catheterization of patients with extensive bronchiectasis limited to one lung has been shown to yield blood from the pulmonary artery on the affected side that was almost arterial in character.[56]

The existence of anastomoses between the bronchopulmonary veins and the pulmonary veins was first described in normal lungs by Zuckerkandl in 1882.[57] The bronchopulmonary veins are usually called bronchial veins, but the former term is preferable because they drain not only the bronchi but also interstitial pulmonary tissue. The smaller bronchi are drained by the pulmonary veins, while the bronchopulmonary veins drain the proximal two to three orders of branches of the trachea and surrounding interstitial tissue. The bronchopulmonary veins drain into the azygos and hemiazygos system, the pulmonary veins into the left atrium. Normally, blood flow across these anastomotic channels is from the pulmonary veins to the bronchopulmonary veins thence to the azygos or hemiazygos veins. The higher pressure in the left atrium than in the right atrium and valves at the site of entrance of the bronchopulmonary veins into the azygos and hemiazygos veins insure this unidirectional flow. The value of these anastomoses is seen where suppuration exists in the lungs, causing thrombosis of pulmonary veins. Then blood is drained away from the area by the bronchopulmonary veins.

In chronic obstructive emphysema great expansion in the extent and size of these anastomotic venous channels has been demonstrated. The causes of this expansion are not completely understood. Liebow[58] has suggested that changes in the respiratory pumping action in chronic obstructive emphysema which affect the truly pulmonary venules to a greater extent than the more protected bronchopulmonary venules might favor this expansion. Bullae have been shown to represent expanded parts of the respiratory tract more proximal than alveoli, and the venous drainage of these structures is by way of the bronchopulmonary veins rather than the pulmonary veins, just as their arterial supply comes from the bronchial arteries. Also, it has been shown that the walls of bullae contain granulation tissue and much smooth muscle. During the formation of granulation tissue these anastomotic channels form and persist even after resolution of cicatrization.

In chronic obstructive emphysema an actual reversal of flow in these expanded channels may occur, so that blood would flow from the bronchopulmonary veins into the pulmonary veins. This might occur particularly in chronic cor pulmonale with right heart failure where the pressure in the azygos-hemiazygos system will exceed that in the pulmonary veins. In addition, dilatation of the bronchopulmonary veins will cause stretching of the valve rings at their connections with the azygos or hemiazygos veins, producing incompetency of these valves. Such reversal of blood flow would tend to cause pollution of systemic arterial blood by desaturated hypercapnic venous blood, and could thus furnish an important proportion of the venous admixture in the arterial blood.

This expansion of the bronchial arterial and bronchopulmonary venous systems in chronic obstructive emphysema has not been quantitatively evaluated in any given case. Nor has it been possible to estimate its relative importance during exercise and at rest. Yet, evidence for its existence should stimulate the development of methods for this type of assessment.

Precapillary anastomoses between pulmonary arteries and the pulmonary veins have been demonstrated in normal man, but they are apparently not extensive enough to be significant.[54] The perfusion of poorly ventilated parts of the lung is equivalent in effect to shunting blood from the pulmonary arterial to the pulmonary venous system. However, this phenomenon is minimized, since blood flow through these areas usually is reduced markedly by all the mechanisms described as causing an increased resistance to blood flow.[21]

2. *Cardiac Output*

The cardiac output in chronic cor pulmonale due to chronic obstructive emphysema has been the subject of some controversy.[5, 9, 60] Some observers have been impressed by the frequency of high cardiac output and others have emphasized the presence of low cardiac output. The cardiac output at any particular

time will depend on the complex interplay of the many variables. It will depend not only on the type and extent of pulmonary disease present but also on the stage in which the patient is being studied, and will thus be affected by the presence of intercurrent acute bronchitis or pneumonitis, the degree of hypoxia, the presence and severity of polycythemia, the blood volume and the presence and degree of heart failure.

The following mechanisms act to increase cardiac output in chronic cor pulmonale. Hypoxia acts directly to increase cardiac output. If polycythemia is present, the associated hypervolemia will also contribute to increased cardiac output. The activity of the inflammatory process in the lung, since bronchopulmonary infection is always present, tends to increase oxygen consumption and, thereby, leads to an increase in cardiac output, even in the absence of fever. The increased muscular work of breathing in chronic obstructive emphysema also disposes to an increased cardiac output.[13] If cardiac failure occurs at a stage during which cardiac output is increased, some fall in cardiac output will occur, but the output may still be higher than normal. The paradox of high output failure may thus be explained by the state of the circulation just preceding failure of the right ventricle.[33, 61] When congestive heart failure is present, an increase in plasma volume also often helps maintain the cardiac output, but later by contributing to the overdistension of the right ventricle may help to lower it.[62] All the factors which tend to increase cardiac output are potentially reversible by intense treatment; a patient in whom cardiac output is high during a desperate stage in his illness may have a normal output after a successful course of treatment.

If the factors described above which tend to increase cardiac output are less marked in extent or of shorter duration, a normal cardiac output may be observed. Cardiac output which was not markedly elevated may be lowered to what is determined as normal cardiac output during a period of moderate right ventricular failure.

A low cardiac output may be observed in chronic cor pulmonale due to chronic obstructive emphysema under various circumstances. Cardiac output may be lowered by severe cardiac failure. If all the factors tending to produce high cardiac output are present, but pulmonary vascular resistance is high (over four times normal), cardiac output will be low. In such cases the vascular bed of the lung has become reduced to such an extent that it acts much like a "tight mitral stenosis" in limiting cardiac output.[32] This marked increase in pulmonary vascular resistance may be due to severe anatomic changes in the lungs associated with chronic obstructive emphysema as described above, or may be due to a complicating disease such as multiple pulmonary emboli.[63]

Since adequate treatment of the bronchopulmonary disease increases the size of the pulmonary vascular bed, as well as reduces hypoxia with its attendant changes, it is difficult to know which abnormality is most responsible for the precipitation of right heart failure. It is quite likely that the relative importance of each factor varies from case to case, and that in some cases therapy is effective mainly because it actually reduces the extent of anatomic restriction of the pulmonary vascular bed.

D. *Pathogenesis of Type II Chronic Cor Pulmonale*

Where chronic cor pulmonale is due to pulmonary disease with the pathology localized mainly in or about the pulmonary vessels the most important factor in pathogenesis is the reduction in caliber of the pulmonary vascular elements. In most of these cases, in the earlier stages, hypoxemia is not present at rest but appears only with exercise, and then mainly because of the factor of alveolar-capillary block. If the patient does not die of pulmonary insufficiency, he may later develop resting hypoxia and sometimes even polycythemia, so that the additional abnormalities will also act to increase the load on the right ventricle as they do in chronic obstructive emphysema.[33]

Chronic cor pulmonale has been recorded in silicosis without significant chronic obstructive emphysema where the silicotic nodules appeared to be located mainly about vascular channels. Here, arterial oxygen desaturation was frequently not present at rest, but appeared only on exercise, and cardiac output tended

to be normal or low. However, chronic cor pulmonale develops much more frequently in silicosis complicated by emphysema and here the changes are like those in chronic cor pulmonale due to chronic obstructive emphysema alone, except that cardiac output tends to be normal or low.[33]

In chronic cor pulmonale occurring in diffuse granulomatosis of the lungs as in sarcoidosis or beryllosis, and in scleroderma, arterial oxygen saturation is found to be normal or only slightly reduced at rest, but falls markedly on exercise. Polycythemia is not common in the early stages perhaps because of the absence of prolonged hypoxia at rest. Yet, in the absence of cardiac failure, cardiac output in these patients is frequently found to be elevated. It has been postulated that this high output in the absence of continual hypoxia is due to the increased metabolism resulting from the active inflammatory granulomata in the lungs, and increased work of breathing. While most of these patients die of pulmonary insufficiency some eventually develop marked arterial oxygen desaturation and right heart failure, at which time cardiac output is found to be low.[33] The pulmonary hypertension in these conditions usually cannot be reversed.

In chronic cor pulmonale due to repeated pulmonary embolization and in that due to primary pulmonary hypertension, the cardiac output tends to be low. This is a result of the very marked increase in pulmonary vascular resistance. In primary pulmonary hypertension, cyanosis and polycythemia usually occur only late in the disease, unless a patent foramen ovale is present, when a right to left shunt through the foramen may occur.[35]

The term "Ayerza's Disease" has been used in many ways in the medical literature. Originally, it was a term used by Arrillago,[64] a pupil of Ayerza, to signify a condition of right heart failure with severe cyanosis and polycythemia ("black cardiac") associated with pulmonary disease presumed to be syphilitic in origin. However, the term has been used to describe everything from chronic cor pulmonale due to chronic obstructive emphysema with secondary pulmonary arteriosclerosis to primary pulmonary hypertension. It would be best dropped from usage.

In patients with chronic pulmonary disease with markedly restricted pulmonary vascular bed, the abrupt development of some pulmonary catastrophe, such as lobar pneumonitis, or massive collapse of a lung, which produces a critical increase in pulmonary vascular resistance, may cause a rapid dilatation of the right ventricle associated with myocardial ischemia and death. The clinical picture, the electrocardiographic changes and the pathologic findings will be those of acute cor pulmonale, although no pulmonary embolization has occurred.[65]

E. *Diagnosis of Chronic Cor Pulmonale*

1. *General Considerations*

The diagnosis of chronic cor pulmonale would be made only in far advanced cases if it were to depend on the detection of right ventricular hypertrophy, since early right ventricular enlargement is almost impossible to recognize. It is only when the examiner has a high index of suspicion and correlates many suggestive findings that the presumptive diagnosis can be made before the disease is far advanced. While the presence of pulmonary hypertension does not necessarily mean that right ventricular hypertrophy has already developed, when it is demonstrable clinically in a patient with chronic obstructive emphysema, right ventricular hypertrophy is usually present.

2. *Clinical Examination*

The existence of chronic cor pulmonale should be suspected in patients with chronic obstructive emphysema of more than minimal degree. By the time arterial blood gas abnormalities become demonstrable, chronic cor pulmonale may be assumed to be present. The presence of secondary polycythemia is thus usually good evidence that right ventricular hypertrophy has already developed.[33] Clubbing of the digits and pulmonary hypertrophic osteoarthropathy do not necessarily indicate the presence of chronic cor pulmonale, since they may occur with very small focal lesions in the lung, such as bronchogenic carcinoma or fibrous mesothelioma.

The presence of overdistended lungs with the accompanying changes in the contour of

the chest make the detection of the usual signs of pulmonary hypertension and right heart enlargement difficult. Thus, the fact that the heart tones are frequently very faint interferes with auscultation of the heart. Changes in the position of the heart as in thoracic deformity and after resectional pulmonary surgery may affect not only the physical findings but also the electrocardiogram and x-ray appearance.[66] One of the earliest direct signs of pulmonary arterial hypertension is accentuation of the second pulmonic sound, often to the extent that it becomes louder than the second aortic sound. Lower sternal dullness, a useful sign of right ventricular enlargement in other types of heart disease, is often absent because of the hyperresonance of the entire chest. A systolic murmur at the pulmonic area is frequently audible, due apparently to dilatation of the main pulmonary artery just distal to the pulmonic valve ring. However, a systolic murmur at the base of the heart is not an infrequent finding in senescence, so that this may be a suggestive sign only in younger patients. In more advanced cases a high pitched, blowing, early diastolic murmur at the pulmonic area may occasionally be heard, presumably due to dilatation of the pulmonic valve ring. Arrhythmias are quite unusual. By the time the usual peripheral signs of right ventricular failure appear, the recognition of right heart involvement becomes easy. Pleural effusions due to congestive failure are rare; if they occur a postpneumonic empyema or pulmonary infarction should be suspected. Moderate elevation of peripheral venous pressure in the absence of congestive heart failure may occur because of the increased intrapleural pressure present in many patients with chronic obstructive emphysema; however, marked elevation of venous pressure is usually a sign of right heart failure.

3. *Roentgenologic Examination*

In general, careful fluoroscopic examination of the cardiac silhouette in the posterior-anterior, in both obliques and in the lateral projection is superior to roentgenograms, although the latter may be valuable for serial studies. Fluoroscopy also offers valuable information regarding pulmonary function at the same time. While roentgenologic signs of chronic cor pulmonale also occur rather late in the course of the disease, they appear earlier than the physical signs.

The earliest abnormality to become apparent is enlargement of the pulmonary artery trunk and its main branches. This abnormal dilatation is due to the pulmonary arterial hypertension, and must be differentiated from the normal prominence of the pulmonary artery trunk in a vertically placed heart which is rotated clockwise about its longitudinal axis. This positional change of the heart is the usual one occurring in chronic obstructive emphysema where the diaphragm is depressed and the lungs are overdistended. In borderline cases, therefore, it is sometimes difficult to know at what point the main pulmonary artery is enlarged, and when its prominence is due merely to rotation of the heart. This enlargement of the pulmonary artery trunk is best seen with the patient in the right anterior oblique position. As the dilatation becomes more marked, it becomes visible as a convexity of the left middle salient in the posteroanterior projection. If the diameter of the right inferior pulmonary artery at its widest point is over fifteen millimeters in the posteroanterior teleroentgenogram, the presence of pulmonary arterial hypertension is strongly suggested, since Schwedel found this relationship to hold in mitral stenosis.[67] Hilar dance is usually not present, since the degree of augmentation of pulmonary blood flow necessary to produce this phenomenon is usually not found in chronic cor pulmonale. Calcification in pulmonary arterial atheromata may rarely be seen.

Hypertrophy alone of the free wall of the right ventricle in chronic cor pulmonale is undetectable roentgenologically; enlargement of the right ventricle becomes visible only when considerable dilatation occurs. As right ventricular dilatation increases it eventually becomes visible as an anterior bulging in the region of the outflow tract of the right ventricle, best seen encroaching on the retrosternal space in the lateral and right anterior oblique views. In the presence of marked left ventricular enlargement, anterior bulging in the right an-

terior oblique view cannot be considered as evidence for right ventricular enlargement, since under these circumstances the left ventricle may encroach on the retrosternal space. In chronic cor pulmonale, an enlarged right ventricle never forms part of the left border of the cardiac silhouette in the poster-anterior projection. However, when enlargement of the right ventricle is marked an increase in the transverse diameter of the heart in the posteroanterior projection may appear; this is due to displacement of the left ventricle, the right ventricle still being anteriorly placed. This is a late development; in most cases of chronic cor pulmonale an increase in the transverse diameter of the heart in the posteroanterior projection does not appear. Displacement of the left ventricle by a markedly enlarged right ventricle so that clearing of the spine does not occur with rotation up to 65 degrees in the left anterior oblique view may also be seen. When congestive failure develops, enlargement of the right atrium and dilatation of the superior vena cava may be observed.

Angiocardiography is not particularly useful for the diagnosis of chronic cor pulmonale but sometimes may be of value in the differential diagnosis if it helps exclude congenital heart disease, or if it discloses an arteriovenous fistula in the lung.

4. *Electrocardiography*

Like all other diagnostic criteria, electrocardiographic abnormalities also occur late. However, they frequently demonstrate alterations as early as the roentgenologic examination. In addition to the usual leads, special precordial leads over the right chest (V_{4R}, V_{5R}) may give valuable additional information.

The changes which are most frequently seen in chronic cor pulmonale due to chronic obstructive emphysema are those which are not themselves pathognomonic of right ventricular hypertrophy. As a result of the overdistended lung and the depressed diaphragm in chronic obstructive emphysema, the heart assumes a more vertical position, and is rotated clockwise about its longitudinal axis, sometimes with backward displacement of its apex. This is usually manifested in a mainly inverted QRS in aV_L and an upright QRS in aV_F, and a shift of the transitional zone over the precordium to the left, with the presence of S waves in all the limb leads and the persistence of S waves in V_5 and V_6. The QRS complexes may sometimes be of low voltage, especially in the precordial leads. This may be due to the increased volume of air-containing lung between the heart and chest wall, or due to a positional change in the heart so that the direction of the QRS vector becomes perpendicular to the frontal plane. All of these changes will often simulate or be exaggerated by the presence of right ventricular hypertrophy or dilatation, since right ventricular enlargement will produce the same kind of rotation of the heart as the pulmonary changes associated with chronic emphysema.[68] When in a patient with chronic obstructive emphysema, P pulmonale is present with these changes, the diagnosis of chronic cor pulmonale becomes extremely likely even though these changes per se are not the result of hypertrophy of the right ventricle.

P pulmonale[68-70] is a tall peaked P wave in leads II, III and aV_F. Usually it is also seen to be small in lead I, inverted in aV_L and often diphasic (plus minus) in V_1 and V_2. It is often associated with a depression of the P-Q segment, due to the prominent negative Tp waves. This is apparently a secondary T-wave change, since it is associated with high voltage upright P waves. In some patients it may revert to normal on treatment. The exact mechanism for its production is unknown. While in some cases it may be associated with hypertrophy or dilatation of the right atrium, it frequently is present when these are absent. In most cases it is probably due to positional change; in a markedly vertical heart with a low diaphragm the apex is displaced in such a way that higher upright P-wave potentials, ordinarily facing towards the back or other parts, are now directed to the feet.

The appearance of an M shaped QRS complex (rsR′), with R′ taller than r, in leads over the right precordium (V_{4R}, V_1 and V_2), which has been called incomplete right bundle branch system block by some, is usually good evidence of right ventricular strain and hence chronic

cor pulmonale. However, it is sometimes difficult to know whether a small R′ in V_1 or V_2 is due to this incomplete right bundle branch system block, or whether it is merely a manifestation of the normal late activation of the pulmonary conus. Indeed, in some cases it is possible that this R′ becomes apparent mainly because of the downward displacement of a vertical heart associated with the low diaphragm which causes V_1 and V_2 to assume a higher position than usual relative to the heart. The normally delayed activation of the pulmonary conus (which may or may not be dilated) now becomes more readily evident. This may explain the observation by Thomas[28] that leads taken in the third left intercostal space (V_2 3ics) may be helpful in indicating the presence of right ventricular strain if they show an R′ taller than 4 mm. This would also explain the occasional transient appearance of rsR′ complexes over the right precordium in acute cor pulmonale where right ventricular hypertrophy cannot have had time to develop.[65] In some cases, complete right bundle branch system block with QRS duration longer than 0.12 second may also result from right ventricular involvement in chronic cor pulmonale.

The presence of a typical right ventricular hypertrophy pattern (a relatively tall late R in aV_R, V_{4R} or V_1) is usually definite evidence of chronic cor pulmonale.[71] The tall R may sometimes be preceded by a tiny Q wave; in such a case, care must be taken that an initial tiny R wave is not being overlooked, since then the complex would be of the rsR′ type.

Our experience suggests that the first type of right ventricular enlargement pattern (rsR′ over the right precordium) occurs somewhat more frequently in chronic cor pulmonale due to chronic obstructive emphysema, and that the second type (tall late R over the right precordium) occurs more often in chronic cor pulmonale due to pulmonary disease with predominant vascular involvement. This may be a manifestation of the greater frequency of augmented input loading of the right ventricle in the first type of chronic cor pulmonale where hypervolemia and increased cardiac output are more common. The relationship between the type of overload on the right ventricle and type of electrocardiographic evidence of heart strain has been described by Donzelot[72] and Cabrera C.[73] For example, in interatrial septal defect an input overload pattern (*surcharge*) is usually seen (rsR′) while in congenital pulmonic stenosis a resistance overload pattern (*barrage*) is usually found (tall R over right and much of left precordium with depressed ST and inverted T). However, this simple relationship is complicated by the fact that in chronic cor pulmonale due to chronic obstructive emphysema, resistance overloading also occurs because of the increase in pulmonary vascular resistance and pressure. Moreover, with the development of right ventricular failure and dilatation of the right ventricle, input overloading occurs even in chronic cor pulmonale of the second type due to pulmonary disease where the pathology is largely localized in or about the pulmonary vessels. Complete evaluation of this difference in incidence of right heart strain pattern await correlative studies of the type of pulmonary disease, the pulmonary vascular resistance and pressure, the blood volume, the degree of hypertrophy and the degree of dilatation of the right ventricle.

Frequently, the presence of a right ventricular strain pattern is associated with the presence of inverted T waves in V_2 through V_4. These often become upright after treatment. The reason for the inversion of these T waves is not fully understood as yet. They may be caused by right ventricular dilatation, reflecting merely an increased clockwise rotation of the heart about its longitudinal axis, acute right heart strain or ischemia of the anterior wall of the heart. That the first mechanism is probably operating most often is borne out by the observation that after successful treatment, some cases demonstrate a shift in the transition zone over the precordium to the right, and a reduction in size of the S waves in the limb leads and in V_5 and V_6. This is not associated with demonstrable change in position of the diaphragm, but there has been abolition of congestive failure and hence presumably a re-

duction in right ventricular dilatation. Absence of a prolonged Q-T interval may help rule out anteroseptal infarction when the T waves are inverted over the right precordium, since it has been reported that the Q-T interval is normal in patients with chronic cor pulmonale in the absence of other types of heart disease.[74]

5. Cardiac Catheterization

Right heart catheterization offers the best method for the early detection of pulmonary hypertension and also may give much additional information about the disturbed hemodynamics in a given case. As yet it cannot be justified as a routine procedure but in some cases, in combination with blood gas studies and pulmonary function tests, it helps greatly in management. Cardiac catheterization on occasion may also be very useful to rule out the presence of a congenital cardiac defect.

There must be a stage in the development of chronic obstructive emphysema when pulmonary hypertension is present before right ventricular hypertrophy has yet occurred. If the clinical picture of chronic obstructive emphysema is typical with regard to the appearance of the lung and by function testing, the presence of pulmonary arterial hypertension at rest is good evidence that hypertrophy of the right ventricle is already present, even though there may be no evidence of this hypertrophy in the electrocardiogram or on fluoroscopy. Early, pulmonary artery pressures may be normal at rest and become elevated only with exercise; later, pulmonary hypertension is present at rest. Often, in a patient with chronic cor pulmonale in congestive failure with marked pulmonary hypertension and increased cardiac output, repeat catheterization after intense pulmonary and cardiac therapy will show the cardiac output to be normal, and the pulmonary artery pressures normal or nearly normal at rest, becoming elevated only with exercise.[33]

In these patients with pulmonary arterial hypertension, Dexter[32] has demonstrated a normal pulmonary arterial wedge pressure. This differentiates the pulmonary hypertension present in chronic obstructive emphysema from that which may be present in patients with mitral stenosis or left ventricular failure where both the pulmonary arterial wedge and the pulmonary arterial pressures are elevated.

In chronic cor pulmonale in congestive failure the administration of digoxin intravenously may cause a paradoxic rise in pulmonary artery pressure. This can be explained by the fact that digoxin causes an increase in cardiac output and probably a better emptying of the failing right ventricle. The resultant increased blood flow through a pulmonary vascular bed which is reduced in size and in distensibility causes a rise in pulmonary artery pressure. Acute digitalization in patients with cardiac failure with chronic pulmonary disease and pulmonary hypertension, but with arteriosclerotic or hypertensive heart disease, causes a fall in pulmonary artery pressure. This thus differentiates pulmonary hypertension due to a reduction in the pulmonary vascular bed and that due to left ventricular failure.[48]

III. Treatment

A. *General Considerations*

Until recently, most reports have emphasized the futile aspects of the treatment of chronic cor pulmonale. This attitude arose mainly because of inadequate treatment of the pulmonary disease. No attempts were made to correlate the variations in response to therapy with the type of pulmonary disease which caused the chronic cor pulmonale; the pathologic physiology of chronic cor pulmonale was incompletely understood, symptoms due to pulmonary disease were not adequately separated from those due to cardiac failure and some of the more helpful technics of therapy of chronic bronchopulmonary disease were not available. Where the chronic cor pulmonale is due to chronic obstructive emphysema and many of the pathologic changes are partially reversible, there is good reason to expect that real improvement will result from treatment. If the chronic cor pulmonale is due to pulmonary disease where the changes localized mainly in or about the pulmonary vessels are mostly irreversible, the outlook for treatment is more dismal.

B. *Treatment of Type I Chronic Cor Pulmonale*

1. *Prophylaxis*

If the specter of chronic cor pulmonale is kept before us, we can realize the need for more intense and careful management of patients with chronic bronchopulmonary disease, especially chronic bronchitis. Recurrent and lingering episodes of bronchitis in patients should be treated vigorously. Their effect may be cumulative and lasting. Climate, poverty and air pollution are undoubtedly of great importance; every attempt should be made to remedy the latter by industrial and social safeguards. When chronic obstructive emphysema is already present, acute respiratory infections should be treated as major illnesses, since the first episode of congestive failure in chronic cor pulmonale usually follows an acute respiratory infection with its invidious sequence of events. Impending circulatory and pulmonary breakdown frequently may be predicted by watching for signs of increasing pulmonary insufficiency, polycythemia and abnormalities in the blood gases.

2. *Active Treatment*

Intensive treatment of the bronchopulmonary disease is as important, and usually more important, than specific cardiac measures. Congestive heart failure can be alleviated only by at least partially reversing many of the pathologic changes in the lung which are responsible for the anatomic reduction in the pulmonary vascular bed and the hypoxia.

The objectives of therapy are to combat infection, produce an adequate airway and improve effective alveolar ventilation. The use of antibiotics orally, by injection, and especially by inhalation are of paramount importance. Bronchodilator drugs are invaluable for aiding in bronchial drainage and improving ventilation.[75] They also help in the control of infection. Patency of airways and resolution of infection are promoted also by the use of sputum liquefiers, correction of dehydration and facilitation of cough and expectoration. Occasionally, bronchial aspiration by catheter or bronchoscope is lifesaving. Pulmonary ventilation can often be markedly improved by breathing exercises; pneumoperitoneum and abdominal belts have been disappointing. In desperate cases and where airway obstruction is very severe, the use of adrenal corticosteroids or corticotropin may be necessary to reduce secretions and bronchial edema; however, their use is fraught with danger because of their effect on the body defenses against infection and because of their tendency to cause salt and water retention.

Treatment of the hypoxia is essential. Although direct treatment with oxygen is hazardous, it is often necessary. Such treatment must be controlled by careful observation of the patient. The respiratory system in these patients is usually nonresponsive to carbon dioxide; the tachypnea may be maintained mainly because of the presence of hypoxemia. Correction of the hypoxemia may lead to hypoventilation with carbon dioxide retention, acidosis and death. If oxygen is administered, it should be given well humidified, in low concentrations, intermittently and only if the patient is under constant observation by a physician, not a nurse; control of the oxygen therapy will depend on its effect on the frequency and depth of respiration, the clinical appearance of the patient and, finally, wherever possible, by serial determinations of the arterial blood gases.[63] The latter technics, while not always available, are nonetheless extremely important, since the clinical appearance of the patient may be deceptive. It is often preferable to use oxygen with some type of mechanical respiratory aid such as a tank-type body respirator to hyperventilate the patient in an attempt to "wash out" retained carbon dioxide at the same time that oxygen is being administered; this may have to be continued over a period of several weeks.[63, 76] It is not sufficiently appreciated that the carbon dioxide stores in the body are not confined to the blood alone, but include those present in all of the body fluids as well.[51] Acetazoleamide (Diamox), a carbonic anhydrase inhibitor, has proved useful in the treatment of respiratory acidosis.[77] Its diuretic action is also valuable. Respiratory depressant drugs, such as morphine, are strongly contraindicated. The usefulness of

intermittent positive pressure breathing apparatus has not been completely evaluated.[78-80]

These patients are critically ill, and their treatment requires meticulous attention to detail. They are frequently somnolent, confused and uncooperative, a result of hypoxia and hypercapnia. Cerebrospinal fluid pressure is often increased,[81] and even papilledema has been observed in many of these patients with hypercapnia.[2] Restoration of alertness is of prime importance, since it will permit more effective coughing and expectoration of sputum and greater cooperation with therapeutic procedures.

Specific cardiac therapy may be effective, if combined with the pulmonary measures just described. Digitalis, contrary to some earlier reports, has been shown definitely to improve cardiac performance in patients with chronic cor pulmonale in congestive failure. It is therefore indicated in the presence of cardiac failure and should be continued indefinitely after the failure has disappeared. Mercurial diuretics and salt restriction are also useful, but electrolyte imbalance should be carefully watched for in these patients. Rest is extremely important to minimize the body's metabolic requirements in the face of pulmonary and circulatory insufficiency. Phlebotomy is an important adjunct to therapy when polycythemia and hypervolemia is present. Both the adaptive significance and the disadvantages of the polycythemia and the hypervolemia have been discussed above. The red blood cells in secondary polycythemia are often hypochromic, so that attention should be paid to the hematocrit as well as the red blood cell count and the hemoglobin.[63] Bleeding is advisable when the hematocrit is above 55; 300 to 500 ml. of blood may be removed every 3 to 5 days to bring the hematocrit down to 50, and the hemoglobin to about 14 Gm. The usefulness of ganglionic blocking agents, such as tetraethylammonium and Priscoline, in lowering pulmonary arterial pressure in chronic cor pulmonale in chronic obstructive emphysema has not been demonstrated.

Many of these patients with chronic cor pulmonale have associated arteriosclerotic or hypertensive heart disease, and while the presence of some degree of left ventricular failure may be difficult to prove, their response to specific cardiac therapy may be especially gratifying.

In our own experience, as well as in that of others,[1] peptic ulcer has been noted to occur with increased frequency in patients with chronic obstructive emphysema with or without polycythemia. Routine examination of the stomach and duodenum is, therefore, indicated. We have also noted an increased frequency of cholelithiasis in those patients who have secondary polycythemia. The development of pain in the right upper quadrant of the abdomen may thus result from acute cholecystitis as well as hepatic congestion associated with right heart failure.

C. *Treatment of Type II Chronic Cor Pulmonale*

Therapy of chronic cor pulmonale in patients with pulmonary disease where the pathology tends to be localized in or about the pulmonary vessels is unsatisfactory. Where bronchopulmonary infection or chronic obstructive emphysema is present as a complication it should be treated intensively. The latter especially may complicate such conditions as silicosis and diffuse pulmonary sarcoidosis. Diffuse pulmonary granulomatosis may be treated with cortisone or corticotropin, but whether resolution or fibrosis of the granulomata will occur in a particular patient cannot be predicted. Cournand has advised marked restriction of physical activity to reduce cardiac work as one of the few helpful procedures available, since the restriction of the pulmonary vascular bed in these patients is largely irreversible. When congestive failure develops, they usually die in a matter of weeks.[63]

Summary

Because of newer technics of treatment, a small but ever increasing number of patients with chronic pulmonary disease are surviving long enough to develop chronic cor pulmonale. An attempt has been made to correlate the newer knowledge of aberrations of cardiocirculatory and respiratory physiology in chronic pulmonary disease.

Respiratory insufficiency may be due to

varying proportions to the following: (1) ventilatory dysfunction or impairment of the ability to move air into or out of the lungs; this may be of two types: (a) obstructive, due primarily to airway narrowing and (b) restrictive, due to disordered function of the thoracic bellows or diminished pulmonary distensibility; (2) unequal distribution of inspired air to the alveoli (intrapulmonary mixing); (3) uneven perfusion or distribution of capillary blood flow; (4) impaired diffusion or transfer of oxygen across the alveolar capillary barrier and (5) impaired cleansing of the lung.

The same abnormal physiologic change may result from pathologic conditions which differ widely in etiology; furthermore, a particular disease may give rise to widely differing functional patterns.

The types of pulmonary disease causing chronic cor pulmonale may be divided into two main categories: (1) Type I, pulmonary diseases associated with chronic diffuse obstructive emphysema. (2) Type II, pulmonary diseases in which the pathologic process tends to be localized in or about the pulmonary vessels. In some instances, a case belongs mainly in one category but may demonstrate some features of the other.

The strain on the right ventricle is a result of: (1) increased resistance to pulmonary blood flow and (2) increased cardiac output (when present). Increased resistance to pulmonary flow may be due to: (a) reduction in caliber and distensibility of the pulmonary vascular bed which may be structural or related to hypoxia, (b) polycythemia and (c) intrapulmonary vascular shunts.

Respiratory insufficiency may be suspected from the history. Physical and roentgenologic examinations may be confirmatory, but pulmonary function tests are necessary for a precise evaluation of the functional abnormalities. The recording of a physiologic, as well as a pathologic diagnosis, is a useful practice in the individual case.

The presence of right ventricular enlargement can only be detected clinically when the chronic cor pulmonale is moderately advanced. However, clinical and roentgenologic evidence of pulmonary hypertension in chronic pulmonary disease indicates that right ventricular hypertrophy is probably present. The electrocardiogram may be helpful even in the absence of a definite right heart strain pattern since the electric position of the heart is often suggestive. Cardiac catheterization provides the best method for the early detection of pulmonary hypertension.

The treatment of chronic cor pulmonale is much more hopeful today than in the past. It is most satisfactory when cor pulmonale is due to pulmonary disease of type I. Intensive therapy of the bronchopulmonary disease is as important as specific cardiac measures. The objectives of therapy are to combat infection, produce an adequate airway and improve effective alveolar ventilation. This may partially reverse many of the pathologic changes in the lung which are responsible for hypoxia and the anatomic reduction in the pulmonary vascular bed.

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SPECIAL COMMITTEE REPORT

Heart Disease Claims under the California Workmen's Compensation Act

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THE Cardiac in Industry Committee of the California Heart Association in 1951 initiated a study of the problem of the causation or aggravation of heart disease by occupational factors. This field seemed particularly pressing because important decisions affecting the employment of persons with heart disease, and in arranging insurance for them, were being based more upon speculation than upon facts. A number of physicians, including some of the Committee, believed that many workmen's compensation claims for heart disease were being made, and that many claimants were being awarded large amounts on tenuous grounds. They felt that an industrial physician could not conscientiously recommend the hiring of a person known to have heart disease because of the excessive "compensation risk."

The Committee recognized the claims files of the California Industrial Accident Commission as a valuable source of information and accordingly asked the Commission for access to its records. Thanks to the fact that the Division of Labor Statistics and Research had for several years been indexing the case records by diagnostic category, it was possible to extract from the files all the heart cases for the four fiscal years 1948–51. This was graciously done by the Commission staff. Funds for professional and clerical help, and special assistance at various stages were provided by the California State Department of Public Health.

The study was aimed at answering the following questions: (1) Is the medical evidence in the records of claimants for workmen's compensation due to heart disease adequate to reach a decision as to the relationship between the work-connected injury and the disease process? (2) Are the Industrial Accident Commission decisions in heart disease cases consistent with expert medical opinion which is rendered outside the claims process? (3) In reaching decisions for heart disease cases, what criteria have been used by the Industrial Accident Commission, and what criteria can be recommended to the Commission for future use with reference to such medical evidence? (4) What is the degree of unanimity of medical opinion with respect to the relationship between alleged "injury" and heart disease? (5) What relationship, if any, exists between the nature of employment and the causation or aggravation of heart disease?

Two physicians were employed by the California Heart Association. They examined the Commission files, and prepared abstracts of the pertinent medical and social data,

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according to an outline provided by the Cardiac in Industry Committee. It should be noted that the record does not always contain the entire body of evidence available for the Industrial Accident Commission decision, oral testimony particularly. While a complete stenographic record is made of the hearings, this record is transcribed only rarely, for some special purpose. Many cases are settled by compromise, and the medical evidence is often not as extensive as in cases settled by decision of the Commission. Some cases are put on the calendar and dropped, with little or nothing in the record. Uncontested cases may show little more medical information than a sentence on the record, such as, "Dropped dead of a heart attack while fighting a fire."

Five hundred and eighty-three heart disease claims were found for the four year period. These were abstracted, and the abstracts were submitted to extensive study. Certain of the cases were rejected for detailed study because of meager medical information. These were 185 in number, and included many cases in which the claim was not pressed, some cases with almost no medical information, and a few cases where heart disease was mentioned but was not the major injury. The balance of the abstracts, 398 in number, were then subjected to detailed study including review by a panel of five physicians in a manner described below.

Tables 1, 2, and 3 describe the entire population of claimants indicating the occupation, age and "severity of occupation." The remainder of the tables pertain only to those cases in which information in the record was adequate for medical review. In tables 1, 2, and 3 cases with adequate medical information are called "reviewed" and those with inadequate information are "decisions not reviewed."

The population as might be expected consisted largely of industrial workers. Table 1 indicates that more than half the claimants were craftsmen, operatives and laborers. About one-fifth were policemen and firemen. All other occupations, including white collar workers, farmers and some types of service workers comprise about one-fourth of the claimants.

TABLE 1.—*Number of Claims by Occupation Group and by Selected Individual Occupations*

Occupation	Total	Reviewed	Not Reviewed
Total	583	398	185
Professionals	33	21	12
Farmers and farm managers	2	2	0
Managers, officials and proprietors	26	18	8
Clerks	14	9	5
Salesmen	18	12	6
Craftsmen	149	116	33
Including:			
Carpenters	32	27	5
Foremen	15	10	5
Auto mechanics	14	11	3
Other mechanics	13	10	3
All other craftsmen	75	58	17
Operatives	84	57	27
Including:			
Truck and tractor drivers	18	11	7
All other operatives	66	46	20
Service workers	140	98	42
Including:			
Firemen	46	35	11
Guards	12	9	3
Policemen	59	41	18
All other service workers	23	13	10
Farm laborers	9	4	5
Other laborers	77	49	28
Not stated	31	12	19

In any consideration of the occupational or compensation aspects of heart disease in California, it is necessary to take into account the effect of statutes* which apply to policemen and firemen, and which in effect establish the presumption that any case of heart disease occurring in these occupations arises out of and in the course of employment, unless there be evidence to the contrary. In view of this presumptive work-connection, special tabulations have been made of the figures concerning policemen and firemen.

A measure of the amount of claim-filing from different occupations may be seen in table 1*A*. It shows the number of claims filed per year for every 100,000 males employed in 1950 in the occupation. The rate of claim filing in different occupations ranges from 103

* Sections 3212 and 3212.5, Labor Code of California.

TABLE 1A.—*Number of Heart Claims per Year per 100,000 Employed Civilian Males* by Occupation Group and by Selected Individual Occupations*

Occupation	Claim Rate per 100,000
Total	5.3
Professionals	3.1
Farmers and farm managers	0.5
Managers, officials and proprietors	1.8
Clerks	1.9
Salemen	2.0
Craftsmen	6.5
Including:	
Carpenters	10.2
Foremen	8.2
Auto mechanics	7.2
Other mechanics	5.1
All other craftsmen	5.5
Operatives	4.7
Including:	
Truck and tractor drivers	5.3
All other operatives	4.5
Service workers	17.6
Including:	
Firemen	103.1
Guards	21.5
Policemen	87.1
All other service workers	3.7
Farm laborers	1.6
Other laborers	9.0
Not stated	—

* From U. S. Bureau of Census: U. S. Census Population, 1950; vol. 11, Characteristics of the Population, part 5, California, chapt. C, table 75. Washington, D. C., U. S. Govt. Printing Office, 1952.

per 100,000 for firemen and 87 for policemen down to 0.5 for farmers and farm managers. It appears that the occupations may be divided into three groups with respect to filing of claims for workmen's compensation due to heart disease. One group consists of those who are completely covered by workmen's compensation and for whom work-connection is presumed in the case of heart disease, i.e., policemen and firemen. The second group includes those largely covered by workmen's compensation and for whom work-connection in the case of heart disease claims must be proved, i.e., industrial workers generally. The third group includes those for whom workmen's compensation coverage is only partial, i.e., farm workers, professionals, and the self-employed. The rates for the first group range from 87 to 103 per 100,000, rates for the second group extend largely from 5 to 10 per 100,000. For the third group the rates are generally less than 3 per 100,000.

It should be kept in mind that these are rates of claims-filing; not of heart disease. The important fact is that of the cases of disabling heart disease which occur, only a few result in Workmen's Compensation claims.

Tables 2 and 2A indicate the age distribution of claimants. Of some interest is the fact that over one-fifth are less than 45 years of age and well over one-half are less than 55 years of age. It may also be seen that the cases reviewed do not differ materially from the total group with respect to age.

The distribution of claimants into occupations grouped according to severity may be seen in tables 3 and 3A. The grouping of occupations is based upon a judgment as to the physical activity usually involved in the occupation. For example, laboring occupations are considered strenuous, firemen and policemen duties moderate and most white collar occupations mild. This judgment was made by an occupational analyst who was unaware of the outcome of the claims. It will be seen

TABLE 2.—*Age Distribution, (Number of cases, reviewed and not reviewed)*

	Total	Age Group					
		Under 35	35–44	45–54	55–64	65 & over	Not stated
Total	583	26	102	228	168	44	15
Reviewed	398	16	67	165	119	30	1
Not reviewed	185	10	35	63	49	14	14

TABLE 2A.—*Age Distribution, (Per cent of cases, reviewed and not reviewed)*

	Total	Age Group					
		Under 35	35–44	45–54	55–64	65 & over	Not stated
Total	100.0%	4.5	17.5	39.1	28.8	7.5	2.6
Reviewed	100.0%	4.0	16.8	41.5	29.9	7.5	0.3
Not reviewed	100.0%	5.4	18.9	34.1	26.5	7.5	7.6

TABLE 3.—*Severity of Occupation, (Number of cases, reviewed and not reviewed)*

	Total	Severity			
		Strenuous	Moderate	Mild	Not classified
Total	583	98	360	89	36
Reviewed	398	58	264	61	15
Not reviewed	185	40	96	28	21

TABLE 3A.—*Severity of Occupation, (Per cent of cases, reviewed and not reviewed for those classified for severity)*

	Total	Severity		
		Strenuous	Moderate	Mild
Total	100.0%	17.9%	65.8%	16.3%
Reviewed	100.0	15.1	69.0	15.9
Not reviewed	100.0	24.4	58.5	17.1

that two-thirds of the claims originated from occupations classified as "moderate," the remainder being about equally distributed between "mild" and "strenuous."

As noted above, for the balance of the study only the 398 claims that were considered adequate for medical review will be considered. It is unfortunate that every claim could not be fully studied, particularly because of indications in table 3 that claimants not reviewed came from somewhat more strenuous occupations than did the reviewed group.

Bearing in mind then that a selection has been made, the granting of awards for workmen's compensation due to heart disease and some of the factors affecting it may be considered. The awards fell into three groups:

(1) "Decision IAOE"–means that a hearing was held and the condition ruled to be an "Injury arising out of Employment."

(2) "Compromise and Release"–means that the insurance company and the claimant agreed on a settlement, which the Commission approved. The Commission might have awarded a smaller amount to the claimant, or even nothing at all, had the procedure been carried to a conclusion by the same processes as in group 1.

(3) "Denied or Dropped"–means either (a) that a hearing was held and the claim denied, or (b) that a claim was filed, but the claimant did not press the claim. These classes are thrown together because of the small numbers of dropped claims that were reviewed.

If one wishes to divide the claim population into only two groups, then the "Decision IAOE" and the "Compromise and Release" may be considered as having "Received Payment" and the "Denied or Dropped" group may be considered as having "Received no Payment." Tables 4 and 4A indicate the causative episode as interpreted by the Committee from the abstract of the Industrial Accident Commission (IAC) record. First of all, the tables show that of the 398 claims reviewed 127 (32 per cent) received payment through a Commission decision, 169 (42 per cent) received payment through a compromise and release, 102 (26 per cent) were denied or dropped the claim. Thus, some payment was given to three-fourths of the claimants. (The selected nature of this group again must be emphasized; of those claimants whose records were not reviewed in detail only about one-third received some payment).

Claimants whose records showed "unusual exertion" had denied or dropped claims only in the proportion of about one-seventh. Unusual exertion was defined as a sudden burst of activity following considerable activity. Claimants whose causative episode was something other than "unusual exertion" had

TABLE 4.—*Causative Episode by Award, (Number of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Total	398	127	169	102
Unusual exertion	81	30	40	11
Physical trauma	41	12	19	10
Neither exertion nor trauma	250	76	97	77
Not classified	26	9	13	4

TABLE 4A.—*Causative Episode by Award, (Per cent of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Total	100.0	31.9	42.5	25.6
Unusual exertion	100.0	37.0	49.4	13.6
Physical trauma	100.0	29.3	46.3	24.4
Neither exertion nor trauma	100.0	30.4	38.8	30.8
Not classified	100.0	34.6	50.0	15.4

claims denied in approximately twice the proportion for those with "unusual exertion."

Seventy-eight cases of unusual exertion and 44 of trauma to the chest were analyzed to see the influence upon the award of the time interval between the alleged causative episode and the onset of symptoms. There were only 10 cases in these two classes together in which the interval was more than 10 days; among these, six awards were favorable to the claimants. Almost five-sixths of the unusual exertion claims had onset of symptoms within six hours of the unusual effort, and seven-eighths of these received payments. Among the trauma cases, three-fourths had symptoms within six hours, and four-fifths of these received payments. While nearly half of the unusual exertion claims and two-thirds of the trauma claims had symptoms immediately, they did not receive payment in higher proportion than those in whom an interval up to six hours was recorded.

Severity of exertion in the occupation is tested for its influence in tables 5 and 5A. Lacking a comparable occupational classification of the whole population of the State, it cannot be said whether heart disease claims arise excessively from any level of activity. It is evident that all levels are well represented. It appears that claims originating from occupations classified as involving mild exertion are more likely to be denied or to be dropped than when the occupation is more strenuous, but the differences are trivial.

The influence of the special law affecting

TABLE 5.—*Severity of Physical Exertion by Award, (Number of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Total	398	127	169	102
Strenuous	58	15	30	13
Moderate	264	96	102	66
Mild	61	12	31	18
Not classified	15	4	6	5

TABLE 5A.—*Severity of Occupation by Award, (Per cent of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Total	100.0	31.9	42.5	25.6
Strenuous	100.0	25.9	51.7	22.4
Moderate	100.0	36.4	38.6	25.0
Mild	100.0	19.7	50.8	29.5
Not classified	100.0	26.7	40.0	33.3

policemen and firemen's claims may be seen in tables 6 and 6A. Firemen received payment in approximately six-sevenths of all cases, and policemen received payment in about two-thirds of all cases. The proportion receiving IAOE awards among these workers is about twice as great as it is for the whole group of reviewed cases.

Most of the claims were made for attacks of heart disease occurring while the claimant was at work. However, the proportion of claims awarded payment in the case of attacks occurring at work did not differ significantly from the proportion awarded payment in cases of heart attacks occurring after working hours. Substantially all of the claims appeared to arise because of heart disease diagnosed as coronary heart disease. Of those claimants for whom a definitive diagnosis was

TABLE 6.—*Policemen and Firemen by Award, (Number of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Firemen	35	22	8	5
Policemen	41	23	3	15

TABLE 6A.—*Policemen and Firemen by Award, (Per cent of cases, reviewed only)*

	Total	Award		
		Received payment		Received no payment
		Decision IAOE	Compromise and release	Denied or dropped
Firemen	100.0	62.8	22.9	14.3
Policemen	100.0	56.1	7.3	36.6

TABLE 7.—*Amount of Payments, (Number of cases, reviewed only)*

		Amount of Payment						
		Weekly payments only	Less than $2000	$2000 to 3999	$4000 to 5999	$6000 to 7999	Over $8000	Not known to have received payment
All cases	398	36	76	57	39	39	1	151

Lump sum payments averaged $3,350. Weekly payments averaged $33. Nine persons received both a lump sum payment and weekly payments.

TABLE 7A.—*Amount of Payments, (Per cent of cases, reviewed only)*

		Amount of Payment						
		Weekly payments only %	Less than $2000	$2000 to 3999	$4000 to 5999	$6000 to 7999	Over $8000	Not known to have received payment
All cases	100%	9.0	19.0	14.3	9.8	9.8	0.3	37.8

on record, only 5 per cent had some diagnosis other than arteriosclerotic coronary heart disease.

The amount of payment received by the claimants is shown in tables 7 and 7*A*. (The discrepancy between the number shown in table 7 as not known to have received payment and the number shown in table 4 as having received no payment arises because of the fact that the amount was not stated for some of those classed in table 4 as having been awarded compensation.) Most of the claims were settled through a lump sum payment, the average amount being $3,350. Where weekly payments were made, these averaged $33 per week.

The 398 cases reviewed were sent for study to a panel of physicians including Board-certified* cardiologists, Board-certified* internists and another group of physicians with experience in heart disease such as the members of the California Society of Internal Medicine. Each abstract was reviewed independently by five physicians selected at random from among those interested and agreeing to cooperate. As noted earlier, the abstract does not contain the whole body of information known to the Industrial Accident Commission. Oral testimony, with its many nuances of expression, was not transcribed in toto in most cases. Hospital records and other documents which were examined by the Industrial Accident Commission were not retained or copied in the files.

Table 8 shows the qualifications of the reviewing physicians and their opinions of the relationship between the work injury and the disease. Of some interest is the fact that the Board-certified physicians were somewhat less likely to judge the disease work-connected than were the physicians who were not certified.

In examining the reviewing physicians' judgments, it became apparent that in many cases the reviewer stated the information to be insufficient for him to judge whether or not heart disease was present. Such a reviewer then made no judgment as to work-connection. Three or more reviewers adjudged the information to be insufficient in 79 out of the 398 cases submitted for review. Eliminating these cases with insufficient information leaves 319 cases which were reviewed and which were found by

* American Medical Specialty Boards.

TABLE 8.—*Qualifications of Reviewers by Their Judgment of the Work-Connection of the Heart Claim, (Number of reviews)*

	Total	Cardiologist	Internist	Not Certified
Total	1990	240	860	890
Positive	786	94	298	394
Undecided	408	44	171	193
Negative	796	102	391	303

TABLE 8A.—*Per cent of Reviews*

	Total	Cardiologist	Internist	Not Certified
Total	100.0	100.0	100.0	100.0
Positive	39.5	39.2	34.6	44.2
Undecided	20.5	18.3	19.9	21.7
Negative	40.0	42.5	45.4	34.0

the majority of the reviewers to contain sufficient information for judgment.

For the 319 cases which were actually reviewed by five physicians the extent of agreement can be seen in table 9. In only 47 of the 319 cases (15 per cent) was there unanimous agreement among the reviewers.

One hundred one abstracts were reviewed a second time by the same reviewer after a time lapse of several months. These were sent out to the same physicians (101) just as if they were abstracts not previously distributed. Only a few of the physicians indicated their realization that the review process itself rather than the cases was the subject of study. The results are shown in table 10; only 70 per cent of the abstracts were judged the same way by reviewers the second time. There was some tendency for the second review to throw more cases into the negative category. Thus the first review gives a positive judgment as to work-connection for 46 cases, an indefinite answer for 16, and negative judgment for 39 cases. The second review by the same physician of this series of 101 abstracts gave 42 positive judgments, 13 indefinite, and 46 negative. It appears that medical judgment as measured by reproducibility on case abstract material is far from reliable.

TABLE 9.—*Amount of Agreement Among Reviewers for Cases Where Three or More Reviewers Say Information is Sufficient*

Number of Reviewers Agreeing	Number of Cases
Out of 5 Reviewers	
5	47
4 only	99
3 only	125
No majority (only 2 agree)	48
	319

TABLE 10.—*Amount of Agreement of Reviewers with Themselves as to Work Causation or Aggravation, (For 101 cases sent to the same reviewer* twice)

All Cases	Total	Reviewer's First Judgment		
		Positive	Indefinite	Negative
Reviewer's *Second* Judgment				
Total	101	46	16	39
Positive	42	34	2	6
Indefinite	13	4	6	3
Negative	46	8	8	30

Table 11 indicates the relationships between the judgment of the reviewing physicians and the award made or the compromise approved by the Industrial Accident Commission. In this connection, it should be pointed out that the Labor Code, itself, in Section 3202 requires the Commission to give a liberal construction of the law for the purpose of extending compensation benefits for protection of persons injured in the course of their employment. This is sometimes referred to as the principle of giving the benefit of any doubt in favor of the employee. It seems appropriate, therefore, to interpret indecision on the part of our medical reviewers as being favorable to the claimant. On this basis, the middle column of table 11 is divided, 28 cases being treated as in agreement with the IAC, and eight not in agreement. Thus we find 205 instances of agreement among the 319 cases, or 64 per cent.

The actual extent of agreement is considerably better than this would indicate, for there are a number of nonmedical factors which may

TABLE 11.—*Association of Reviewer's Group Judgments with Industrial Accident Commission Awards, (All reviewed cases with sufficient information, number of cases)*

	Majority Judgment			
	Positive	No decision	Negative	Total
Industrial Accident Commission Award				
Money awarded....	127	28	88	243
Money not awarded.	18	8	50	76
Total.....	145	36	138	319

be decisive in these cases. The physician reviewers were not called upon to make any legal interpretations, of course. In an attempt to estimate the extent of these nonmedical factors, after the data of table 11 had been collected, the original files were again reviewed in 49 cases of "disagreement" between physicians and the Commission. (These were the files of all such cases handled at the San Francisco office.)

It was observed that some of the awards or compromises gave relatively small amounts to the applicants; in an extreme case, a compromise of $300 was approved, with the comment, "The settlement is on the expressed basis of constituting a goodwill gesture to the widow . . . ." In other cases, compromises were encouraged by Referees, with notes such as: "Heart cases give rise to a good deal of litigation and dissatisfaction, and I suggested to the parties that an attempt be made to settle." In several instances, the question of causal relationship was not before the Commission, it having been stipulated that the heart disability arose out of the work, or the case came under the policemen and firemen provisions, previously mentioned. Several cases resulted in awards to the claimants, but, although heart disease was an issue, the award was based on some other injury. In one such case, there was a specific denial of work-connected heart disease.

Considering these factors, the "disagreements" were categorized as follows:

	Number	Per Cent
Unmitigated disagreements.....	23	47
Awards and compromises less than $1,000..... 8		
Awards and compromises more than $1,000.....15		
Apparent disagreements in which medical testimony left Referee no alternative.....	11	23
Apparent disagreements in which causal relationship was stipulated.....	10	20
Apparent disagreements in which award was actually not based on heart disease*.....	5	10
	49	100

Thus, if it be assumed that these 49 Northern California cases are fairly representative of the whole series, the instances of "disagreement" would be reduced by half, even without making allowance for the compromises and awards to claimants which were made on a compassionate basis or in which payment was made in order to end a disagreeable, unprofitable proceeding in which the causal relationship was neither clearly demonstrable nor disproved.

Some attention should be given to the cases in which the Referee was moved to award benefits to claimants because of what appeared to be a statement of a physician which appeared to be casual, but which nevertheless established a reasonable doubt of work-connection. For example, in a report about a man who sustained myocardial infarction, three months after an injury to the lateral chest wall in which there was no other opinion as to work-connection expressed, a prominent internist concluded: "It is noteworthy that this man had no symptoms of cardiorespiratory disease prior to his chest injury." Despite a strongly-worded opinion from another prominent internist denying any work-connection, the Referee recommended an award for the claimant, quoting the foregoing sentence. Other instances were seen in which physicians made unsupported generalizations or passing comments which reflected

* These cases properly belong in the present study because occupational heart disease was alleged along with other causes of disability.

little thought or study, but which had to be given some weight by the Referees because they were the stated opinions of physicians, all of whom are acknowledged by the courts as experts in matters of disease.

The study indicates that the number of heart disease claims, filed in the period 1948–1951 (583 in four years), was not very great in comparison to the size of the State's population and the number of deaths caused by heart disease. Heart claims constitute about 1.7 per cent of all claims decided by the Industrial Accident Commission, and this proportion has remained quite stable for the period 1951–1954.

There is some discrepancy between the judgments of the California Industrial Accident Commission and a group of expert physicians reviewing the cases in abstract form, but it compares favorably with the substantial discrepancy among the physicians themselves, and the discrepancy between one judgment by a physician and a second judgment made on the same case by the same physician, some time later. Inasmuch as awards favorable to the claimant must be supported in nearly every case by medical evidence, it appears that education of physicians for the part they play in these proceedings is needed.

It may also be pointed out that the allegation that "every heart claim gets an award" has not been substantiated by this study.

ABSTRACTS

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PATHOLOGIC PHYSIOLOGY

Bell, A. L. L. Jr., Smith, C. N. and Andreae, E.: Effects of the Carbonic Anhydrase Inhibitor "6063" (Diamox) on Respiration and Electrolyte Metabolism of Patients with Respiratory Acidosis. Am. J. Med. **18:** 536 (April), 1955.

The effects of Diamox on respiratory variables and urinary excretion were observed in 7 cases of pulmonary emphysema with chronic CO_2 retention. In most instances Diamox induced a copious diuresis of alkaline urine containing large quantities of sodium, potassium and bicarbonate. With continuous administration of the drug, the urinary excretion pattern reverted to control values within a few days, but metabolic acidosis (plasma bicarbonate and pH decreased below control values), and the "dry weight" of the patient persisted throughout the period of drug administration. The administration of Diamox resulted in improved alveolar ventilation as measured by increased PO_2 and decreased pCO_2 after three days of continued dosage. Increase in alveolar ventilation occurred without a consistent increase in minute ventilation, but was always associated with significant diuresis. Increased alveolar ventilation, as indicated by increased PO_2, was noted within four hours after a large, oral dose of Diamox, although the pCO_2 of arterial blood increased during this period. This elevation of pCO_2 in the presence of increased alveolar ventilation is considered evidence for inhibition of carbonic anhydrase activity of the red cell. Most patients exhibited some symptomatic improvement for about two weeks on the drug, followed by return of pretreatment symptoms. In two severely ill patients, Diamox failed to produce significant improvement in the blood abnormalities, and did not alter the fatal course of their respiratory acidosis.

HARRIS

Roberts, K. E., Randall, H. T., Sanders, H. L. and Hood, M.: Effects of Potassium on Renal Tubular Reabsorption of Bicarbonate. J. Clin. Invest. **34:** 666 (May), 1955.

Potassium deprivation may result in plasma alkalosis with an acid urine, and excess potassium administration may produce a plasma acidosis and alkaline urine. To investigate these changes further, the authors studied renal hemodynamics and metabolism in 10 human beings and 6 dogs.

It was found that hypokalemic patients have an increased tubular reabsorption of bicarbonate which could not be explained by elevations of plasma carbon dioxide tension. The enhanced bicarbonate reabsorption contributes to the plasma alkalosis associated with potassium depletion. Administration of KCl in dogs will decrease bicarbonate reabsorption irrespective of changes in glomerular filtration rate.

It appears that K and pCO_2 affect the renal tubular bicarbonate reabsorption independently, and there is indirect evidence that a relative change in pH within the renal tubular cells may be the common denominator of these changes.

WAIFE

McGuire, J. S., Jr., and Lipsky, S. R.: The Effects of Squalene on the Incorporation of Acetate into Plasma Cholesterol in Man. J. Clin. Invest. **34:** 704 (May), 1955.

Squalene is an unsaturated hydrocarbon found in shark liver and human skin and sebum. There is evidence that squalene is a cholesterol precursor. In this study cholesterol metabolism was studied in 8 patients with carcinoma who also received labeled sodium acetate. It was found that the daily administration of 4 per cent squalene resulted in a 2 to 23-fold depression in plasma cholesterol synthesis from acetate. This suppression of the incorporation of acetate into cholesterol is probably due to dilution of a "higher intermediate" pool between acetate and

cholesterol, thus displacing acetate as a source of cholesterol. Squalene also seems to increase, by "piling up," hepatic cholesterol a process which may evoke a homeostatic reduction in cholesterol synthesis from all sources.

WAIFE

Mateer, F. M., Greenman, L. and Danowski, T. S.: Hemodialysis of the Uremic Child. Am. J. Dis. Child. **89:** 645 (June), 1955.

This report summarizes the experiences the authors have had in treating five children with renal disease by means of the artificial kidney. One child had a reversible renal lesion, complete anuria as a result of acute tubular necrosis following treatment of diarrhea with Sulfasuxidine. The other children had various forms of irreversible renal damage; namely, terminal glomerulonephritis, acute cortical necrosis and periarteritis nodosa. The procedures used are fully described and well outlined, and tabled figures are given for the careful measurements made of the appropriate blood chemical studies performed. Improvement occurred in all patients who were stuporous and sitting at the beginning of dialysis. The improvement was transient in only three, however, and these three patients later died. All the reasons for improvement are not clearly understood, but the authors point out one clearly, the effect of the dialysis on hyperkalemia. Very striking electrocardiograms show clearly the improvement effected by removing the serum potassium. In one patient the potassium level rose to 10 mEq./L. The electrocardiogram showed typical changes with absent P waves, widened QRS complex and high-peaked T waves. Following one and one-half hours of dialysis, the electrocardiogram had returned to normal and the K-level fell to 6 mEq./L.

HARVEY

Danzig, L. E., Capt. (MC), U. S. Army, and Kringel, A. J.: Use of the Artificial Kidney in Treatment of Thiocyanate Psychosis. J.A.M.A. **158:** 560 (June 18), 1955.

Potassium and sodium thiocyanate have been used in the treatment of hypertension since their introduction to clinical medicine in 1903. Thiocyanate psychosis is attended by high mortality, and active measures should be taken to eliminate the drug from the body as promptly as possible. A case of this psychosis is reported and was treated by dialysis with the artificial kidney. During a six-hour dialysis, the serum thiocyanate level was reduced from 24.8 to 1.5 Gm. per 100 ml. and 22 hours later the patient's mental condition improved noticeably. She went on to a complete and uneventful recovery. This method should be considered the preferred treatment in all cases of thiocyanate intoxication.

KITCHELL

Gorlin, R., McMillan, I. K. R., Meed, W. E., Matthews, M. B. and Daley, R.: Dynamics of the Circulation in Aortic Valvular Disease. Am. J. Med. **18:** 855 (June), 1955.

Analysis of the results of cardiac catheterization, in 24 patients with aortic valvular disease, indicates an aperture of 0.5 cm.^{2} is critical, if stenosis alone is present, 1.5 cm.^{2}, if combined with insufficiency. Regurgitant valvular apertures of only 0.3 to 0.5 cm.^{2} were associated with regurgitation of 2 to 5 L./min. because of the large regurgitant pressure gradient during diastole; left ventricular stroke work was increased thereby 2 to 4 times. In the presence of a stenotic aortic lesion, work could not increase on effort despite changes in left ventricular filling pressure. Proper interpretation of blood pressure findings in the differential diagnosis of aortic stenosis versus insufficiency includes consideration of the age of the patient, arterial elasticity, presence or absence of congestive failure, presence or absence of peripheral vasodilatation and the heart rate. The life course of patients with aortic stenosis may be conveniently divided into four stages of progression: (1) no clinical or physiologic abnormality, (2) altered left ventricular work response but no clinical abnormality, (3) altered left ventricular work response, decreased output, steeply rising diastolic filling pressures and clinical symptoms of dyspnea, angina and syncope and (4) terminal left and right heart failure.

HARRIS

Abelmann, W. H., Kowalski, H. J. and McNeely, W. F.: The Hemodynamic Response to Exercise in Patients with Laennec's Cirrhosis. J. Clin. Invest. **34:** 690 (May), 1955.

Hemodynamic studies were performed on 11 patients with Laennec's cirrhosis, at rest and during exercise in the supine position. The cardiac output was often high at rest and the peripheral vascular resistance was low. During exercise, the cardiac output increased and peripheral resistance decreased in most cases. These changes were of the order of that seen in normal individuals under comparable conditions. Although the incidence of "high output state" was high, there was no evidence of "high output failure" such as has been described in beriberi heart disease. On the whole, the response of this series of patients with chronic alcoholism and Laennec's cirrhosis to mild and moderate exercise appears to be within normal limits.

WAIFE

Elster, S. K., Horn, H. and Tuchman, L. R.: Cardiac Hypertrophy and Insufficiency of Unknown Etiology. Am. J. Med. **18:** 900 (June), 1955.

Ten cases of cardiac hypertrophy and myocardial failure of unknown origin are presented. Conventional etiologic factors were excluded. The clinical

course of these patients was rapidly progressive, fatal and frequently complicated by recurrent pulmonary and systemic thromboembolism. At necropsy, the hearts showed striking hypertrophy. Degenerative muscular changes, focal necrosis and patchy fibrosis were found predominantly subendocardially and endocardially, frequently associated with mural thrombosis. There were no significant abnormalities of the pericardium, coronary artery tree, cardiac valves or aorta. Myocardial anoxia, a concomitant of the considerable hypertrophy and dilation, is believed to be an important factor in the intensification of the intracardiac abnormality. There is no satisfactory explanation for the initiation of the process.

The majority of the 10 patients were young to middle aged males. In seven cases, symptoms were present for less than six months before the patients sought medical attention. Eight succumbed within 18 months following the onset of symptoms. All patients succumbed with the clinical picture of intractable congestive heart failure. This entity should be considered in all cases of cardiac hypertrophy when a conventional etiology cannot be established.

HARRIS

PHARMACOLOGY

Loewi, O.: On the Mechanism of the Positive Inotropic Action of Fluoride, Oleate and Calcium on the Frog's Heart. J. Pharmacol. & Exper. Therap. **114:** 90 (May), 1955.

Small doses of fluoride cause an increase of the amplitude of contraction of the frog's heart. To find an explanation for this unexpected effect, it proved necessary to investigate the positive inotropic action of calcium and oleate ions.

Isolated frogs' hearts, perfused with Ringer's solution, were utilized. NaF and Ca^{++} restored the normal contractile height after they were depressed by various methods. The fact that it is difficult to wash the fluoride effect away indicates that this ion is fixed to the heart. However, if there is little Ca^{++} in the Ringer's, then it is easy to flush out the fluoride effect. From these results, it is suggested that Ca^{++} and F^{-} form a non-diffusible complex with some cellular component at the cell surface.

Lipoids or oleate have been shown to relieve heart depression. This fact was confirmed in the present study. The effects of fluoride and oleate are qualitatively similar, and their mechanism of action may be similar. Fixation by the heart appears to be a necessary condition for their augmenter actions. Fluoride and oleate relieve depression that may also be relieved by Ca^{++} increase, or that is caused by Ca^{++} excess. It is concluded that the state of the cell membrane is impaired in cardiac depression and that oleate and fluoride restore the normal state of the membrane and thereby the calcium sensitivity.

WECHSLER

Rand, M., Stafford, A. and Thorp, R. H.: The Potentiation of the Action of Adenosine on the Guinea Pig Heart by Ouabain. J. Pharmacol. & Exper. Therap. **114:** 119 (May), 1955.

Previous work has indicated that cardiac glycosides prevent the destruction of adenosine-containing compounds and their loss from the heart. Adenyl compounds, in addition to their biochemical effects of energy transfer, have pharmacologic effects including bradycardia, heart block, coronary vasodilatation, and a beneficial effect on the heart muscle. It was thought that these pharmacologic effects of the adenyl compounds may be concerned with the mode of action of cardiac glycosides. Therefore, this study noted the electrocardiographic changes produced in the guinea pig, and the way in which they were influenced by ouabain.

Standard limb lead II, or chest leads, were recorded before and after the intra-atrial injection every 1 to 3 minutes of small amounts of adenosine solution in anesthetized guinea pigs. Ouabain (10 to 150 μg. (Kg.) was injected into the jugular vein as a single injection or continuously (2 to 12 μg./Kg./min.).

Adenosine produced bradycardia, prolonged PR interval and heart block. The duration of these effects varied with the dose. A single injection of ouabain increased the response to a fixed dose of adenosine to a maximum of tenfold. The continuous injection of ouabain produced electrocardiographic changes similar to ouabain toxicity at pretoxic ouabain levels. Adenosine failed to produce changes when toxic doses of ouabain were administered.

The potentiation of the pharmacologic action of adenosine on the guinea pig heart by ouabain could be explained by the inhibition of an adenyl deaminating system, which usually destroys energy carrying adenosine compounds.

WECHSLER

Baker, W. W. and Baker, J. M.: Ouabainization of the Isolated Frog Heart. Arch. internat. pharmacodyn. **52:** 105 (June), 1955.

A simple and readily controllable method, using isolated frog heart to study the degree of ouabainization, is presented. Electrocardiograms were taken of the perfused heart, showing the stages of ouabainization; namely, a latent period with no change, a reversible period during which T-wave inversion occurs, and another phase during which the glycoside becomes fixed to the tissues and the electric systole is shortened. These phases are reversible when the heart is thoroughly washed. The irreversible phases follow this third phase if ouabainization is continued with the development of a toxic phase characterized by biphasic Q-R-S complexes, and a terminal phase during which there is complete block of all electric activity.

HARVEY

Cáceres, C. A. and Stauffer, J. C.: Mercurialism: Report of a Case Due to Oral Ingestion of a Mercurial Diuretic. New England J. Med. **253:** 55 (July 14), 1955.

This report is concerned with a woman, aged 73 years, who received one tablet daily of chloromerodin (Neohydrin) for eleven months as a part of her treatment for congestive heart failure. Parenteral mercurial diuretics were given only eight times at the very beginning of this period. The patient was admitted with sore gums, ashen-gray lesions of the buccal mucosa, a mercury line on the gums, increased salivation, a metallic taste and transient elevation of the blood nonprotein nitrogen suggesting renal impairment. Except for anorexia there were no gastrointestinal complaints. The urinary mercury level two weeks after the patient had been off all mercurial medication was 1.7 mg./L. Although presumably rare, it is mentioned that mercury poisoning as a result of long-term oral mercurial diuretic treatment must be kept in mind; frequent examinations of the urine and blood nonprotein nitrogen are recommended for its detection.

ROSENBAUM

Moyer, J. H., McConn, R. and Morris, G. C.: Effect of Controlled Hypotension with Pendiomid (as used in surgery) on Renal Hemodynamics and Water Electrolyte Excretion—A Comparison with Hexamethonium and Arfonad and the Effect of Norepinephrine on These Responses. Anesthesiology **16:** 355 (May), 1955.

The present investigation was undertaken to evaluate the renal hemodynamic response to controlled hypotension as it is employed during surgery to maintain hemostasis. Observations of renal function (glomerular filtration rate and renal plasma flow) and of water and electrolyte excretion were made on nine normotensive patients, subjected to two hours of continuous hypotension maintained with pendiomid. Each patient served as his own control for the various studies. After the study period the blood pressure was raised by norepinephrine, while ganglionic blockade was continued with pendiomid, and additional determinations then performed.

The initial depression of blood pressure observed with pendiomid frequently was associated with a sharp depression in renal blood flow and an increase in renal vasoconstriction, which usually corrected itself as the infusion continued; as the blood pressure decreased, the glomerular filtration rate was moderately reduced and there was a significant initial and sustained reduction in water excretion. There was a parallel reduction in sodium excretion. Potassium excretion initially was depressed but then rose towards control levels despite a maintenance reduction in blood pressure. When the blood pressure was increased to control levels with norepinephrine, the glomerular filtration rate returned to its previous levels in all except one case. This indicates that the reduction of glomerular filtration rate resulted from the hypotension rather than from a specific renal vascular effect of pendiomid. There was only a slight increase in water excretion and a greater increase in sodium excretion when norepinephrine was added, but potassium excretion was not altered.

The renal hemodynamic response to pendiomid is similar to that observed with hexamethonium, and is not as marked as following the administration of Arfonad. The observed reduction in glomerular filtration rate is of little significance except in that it leads to a retention of sodium and water. The differences observed between Arfonad and the other ganglionic blocking agents probably are due to the greater reduction in blood pressure obtained with Arfonad rather than to any specificity of action of the drugs.

SAGALL

Kezdi, P. and Hilker, R. R. J.: Local Application of Epinephrine to Carotid Sinus. Arch. Int. Med. **95:** 720 (May), 1955.

Patients with hypertension had an exaggerated response to the Valsalva maneuver, and only 35 per cent of them developed subsequent bradycardia, as compared with 92 per cent of the normals studied. Local application of epinephrine to the carotid sinus of hypertensive patients modified their hyperreactor response as measured by the overshoot in the Valsalva maneuver. Local application of epinephrine to the carotid sinus lowered blood pressure in all hypertensive patients studied by a significant amount for periods lasting up to three hours. It is possible that the increased sympathetic outflow in essential hypertension is caused by an impaired buffer nerve mechanism due to dilatation, abnormal relaxation and decreased pulsatile expansion (loss of elasticity) of the barosensitive arterial walls. This may be a fundamental defect in essential hypertension.

BERNSTEIN

Weil, M. H. and Spink, W. W.: Clinical Studies on a Vasopressor Agent: Metaraminol (Aramine) 1. Observations in Normotensive Subjects. Am. J. M. Sc. **229:** 661 (June), 1955.

A potent vasopressor agent which will not cause local tissue damage at the site of injection such as occurs with norepinephrine in some cases is desirable for treatment of shock, particularly that due to bacteremia. An evaluation of metaraminol was undertaken in 31 normal subjects to record its effect upon blood pressure and pulse rate and to observe local reactions after subcutaneous, intramuscular and intravenous administration. Administration of the drug by any of the 3 parenteral routes produced no demonstrable injury at the site of injection. A prompt and potent vasopressor response was obtained with a single intravenous injection of 3 to 10 mg. With the blood pressure sustained by an infusion of 30 to 200 mg./L. of fluid, subsequent suppor

may be afforded by subcutaneous injections of the drug. The latter route provides an equally potent and more prolonged effect and is preferred over the intramuscular route. The drug may produce a vagotonic effect with depression of sinus node and atrial conduction; this action may be blocked with atropine. No significant toxic effects are recorded. It is concluded that metaraminol is an effective pressor agent for intravenous and subcutaneous use offering certain advantages in the care of patients in shock.

SHUMAN

Lobbin, S. R., Goldfein, S., Schwartz, M. J. and Dack, S.: Adams-Stokes syndrome. The Treatment of Ventricular Systole, Ventricular Tachycardia and Ventricular Fibrillation Associated with Complete Heart Block. Am. J. Med. **18:** 577 (April), 1955.

Four cases of heart block with Stokes-Adams syndrome are presented to illustrate the two different mechanisms which may precipitate the attacks, namely, ventricular asystole and ventricular tachycardia or fibrillation. Treatment should be individualized and adjusted according to the underlying mechanism. Epinephrine is the drug of choice for the treatment of ventricular asystole, and should be administered in sufficient dosage under electrocardiographic control. It is contraindicated when ventricular tachycardia or fibrillation is the mechanism for the attacks. Procaine amide and quinidine have been found ineffective and even harmful in the treatment of ventricular tachycardia or fibrillation in the presence of heart block due to their depressant effect on the junctional tissues. The effect of isopropyl norepinephrine (Isuprel) in two cases of Stokes-Adams syndrome is described. In one case, the causal mechanism was ventricular asystole and in the other, ventricular fibrillation. Isuprel stimulates the higher ventricular centers and therefore does not predispose to ventricular fibrillation. It appears to be the drug of choice when the basic mechanism for the Stokes-Adams syndrome is ventricular tachycardia or fibrillation and when ventricular asystole alternates with tachycardia or fibrillation in the same person. The usual dose for the prevention of attacks is 10–15 mg. sublingually, 4 to 5 times daily. For treatment during attacks, the frequency of administration and the dosage must be increased, depending upon the patient's tolerance and requirements. Three of the cases exhibited atrial flutter in association with the A-V block, a rare combination.

HARRIS

PHYSICAL SIGNS

Palmer, E. D.: Dysphagia Lusoria: Clinical Aspects in the Adult. Ann. Int. Med. **42:** 1173 (June), 1955.

Dysphagia lusoria is the term which for years has been applied to symptomatic esophageal compression by an arteria lusoria. An arteria lusoria is an anomalous form of the right subclavian artery. It arises as the fourth branch of an otherwise normal aortic arch, and passes around the left and posterior aspects of trachea and esophagus, before coming to lie in the proper position to serve as the subclavian artery. This appears to be the most common anomaly of the aortic arch system. Embryologically, an arteria lusoria represents the persisting distal descending portion of the fourth right branchial arch, there having been obliteration of the proximal arch, in reverse of the normal situation. The arteria lusoria, then, takes off directly from the aortic arch, just beyond the origin of the left subclavian artery. The first portion of the arteria lusoria is often dilated at its origin, this representing the remnant of the posterior branch of the right aortic arch. The roentgen signs of pressure upon the esophagus, usually best studied in the right anterior oblique projection, are those of a pulsating oblique extrinsic pressure defect passing upward from left to right, just above an aortic knob impression which at times is unusually small. Each of 11 patients with this anomaly sought help primarily because of dysphagia. Three patients stated that the onset had seemed rather sudden, while the others were not able to state exactly when they had first noticed swallowing difficulty. Three patients had been in the third decade of life when the first trouble was experienced, two in the fourth decade, three in the fifth and one each in the sixth, seventh and eighth decades. One patient had had unexplained spells of choking and syncope when a small child. Seven had been symptomatic more than a year at the time the diagnosis was established, and one had had symptoms for 10 years. The three features which were regularly reiterated during the interviews were disability, fear and fatigue. The dysphagia as described by all of the patients was the simple sensation of temporary arrest of solid boli beneath the manubrium. There was difficulty with liquids if they were taken rapidly. There was no pain other than the discomfort of substernal fullness which regularly accompanies obstructed swallowing. The dysphagia was a constant, daily problem. Physical examination gave no findings which could be ascribed to the anomaly or its effects. The diagnoses were established by the characteristic esophageal defect as demonstrated roentgenologically. Although dysphagia lusoria is a clear-cut mechanical problem which is cured with assurance by resection of the physiologically expendable arterial segment, operative treatment was decided against in all cases. When the very slowly progressive nature of the course of the disease and the absence of complications were balanced against the seriousness of the operation, it was concluded that surgical treatment should be withheld, pending nonoperative therapeutic efforts. Detailed explanations of the x-ray films to the patient and reassurance proved to be effective therapeutic gestures.

WENDKOS

Farringer, J. L., Jr.: Cardiac Tamponade. Ann. Surg. **141:** 437 (April), 1955.

The author studied a group of 30 patients with cardiac tamponade following intrapericardial wounds. Delay in diagnosis or failure to make the correct diagnosis played the major role in 7 of the 11 deaths in the series. Of the 23 in whom tamponade was promptly recognized and upon whom treatment was immediately begun, 19 survived.

It was the author's opinion that since pericardial aspirations can be readily performed, and in the majority of cases will prove sufficient for the recovery of the patient, the regimen of choice should be immediate pericardiocentesis, supportive measures with intravenous fluids, and close observation. Cardiorrhaphy should be reserved for those patients who exhibit a continuing tendency to relapse because of recurring intrapericardial bleeding.

ABRAMSON

Schechter, M. M. and Ziskind, M. M.: The Superior Vena Cava Syndrome. Therapeutic Considerations. Am. J. Med. **18:** 561 (April), 1955.

Twenty-one patients with superior vena cava obstruction were studied during life, and 19 were followed to necropsy. The majority had infiltrative tumors, primarily bronchogenic carcinoma. Treatment was disappointing in this group. Of 17 patients, 11 failed to improve. In all 17 patients, the block persisted despite intensive treatment. Persistence of vena caval block in bronchogenic carcinoma depends upon infiltration of the vascular wall. If compression of the superior vena cava by involved lymph nodes occurs, it is a rare finding. There is no place for surgical therapy in the treatment of the syndrome when it is due to an infiltrative tumor. If radiotherapy or chemotherapy is used, it should be for its effect upon the primary tumor, and secondarily to help preserve the collateral circulation. These forms of therapy will not relieve the obstruction when it is due to infiltration of the vein wall. Excision of a mass producing compression, such as an aneurysm, gives relief of the syndrome unless secondary thrombosis has occurred. The effectiveness of therapy in this syndrome depends entirely upon the underlying disease process. Even though the venous obstruction may persist, the natural tendency is for the symptoms and most of the signs slowly to be relieved spontaneously by the formation of collateral vessels.

HARRIS

Groom, D. and Boone, J. A.: The "Dove-Coo" Murmur and Murmurs Heard at a Distance from the Chest Wall. Ann. Int. Med. **42:** 1214 (June), 1955.

A calibrated, electronic type of heart sound pickup for use in direct contact with the chest wall has recently been developed in collaboration with the General Motors Research Laboratories. This pickup was designed primarily for low (subaudible) frequency vibrations, but is capable of reproduction of sounds up to 500 c.p.s. Used in conjunction with a cathode ray oscilloscope and camera, it records the wave form of heart sounds and murmurs in considerable detail. This technic of electronic reproduction was employed in the study of the dove-coo murmurs of two cases of aortic insufficiency. It was observed that the intensity of the higher frequency components of a murmur is a far more significant factor in determining its degree of audibility than is the overall intensity of the murmur. And the dove-coo, like the whirring, clicking, splashing or churning sounds, all of which may be assumed to have prominent constituents in the higher frequency range as well as high overall intensity, would consequently be heard at a distance from the precordium.

WENDKOS

PHYSIOLOGY

Cooper, K., Edholm, O. and Mottram, R.: The Blood Flow in Skin and Muscle of the Human Forearm. J. Physiol. **128:** 258 (May), 1955.

The introduction of the adrenaline iontophoresis method (Barcroft and associates, 1943) for measuring skin blood flow has made it possible to correlate skin and total forearm blood flow. Forearm blood flow measured by means of a water-filled venous occlusion plethysmograph, was accomplished in human subjects before and after iontophoresis of the skin of the forearm with adrenalin. This adrenalin iontophoresis was shown to arrest skin circulation by the failure of reactive hyperemia to occur in the area during its immersion in hot water. In addition the post iontophoresis arm flow was reduced. The difference in the pre and post iontophoresis arm flows was taken as skin blood flow.

The values varied greatly. Resting levels of forearm blood flow varied from 1.5 to 10.5 ml./100 ml. forearm/min., muscle blood flow from 1.8 to 9.6 ml./100 ml. muscle/min. and skin blood flow from 0 to 70.5 ml./100 ml. skin/min.

WECHSLER

Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., Therman, P-O. G. and Kety, S. S.: The Effects of Sleep and Lack of Sleep on the Cerebral Circulation and Metabolism of Normal Young Men. J. Clin. Invest. **34:** 1092 (July), 1955.

The mysterious mechanism of sleep has been ascribed to anoxemia, cerebral ischemia or narcosis due to metabolic alteration. However, few studies on cerebral hemodynamics and metabolism have been performed. Young healthy male volunteers were studied by the nitrous oxide technic. They were kept awake for 20 hours and the studies were performed under conditions conducive to sleep. No hypnotics were used. The subjects were considered asleep when characteristic patterns were present on the continuous electroencephalogram. Out of 50 attempts to achieve an uninterrupted sleep of sufficient depth and duration, only 6 were successful.

The data reveal that the cerebral blood flow increases in sleep (from 59 to 65 ml./100 Gm./min.). There was a significant decrease in cerebral vascular resistance and arterial blood pressure. No changes in cerebral oxygen consumption or arterial oxygen content were seen. Respiratory acidosis did occur in the absence of sleep, and sleep caused little if any change in CO_2 tension or blood pH. The results raise the question of whether sleep can occur in the absence of respiratory acidosis.

These studies weaken the hypotheses that sleep is produced by arterial anoxemia, cerebral ischemia, depressed cerebral metabolism or generalized narcosis.

WAIFE

Sokoloff, L., Mangold, R., Wechsler, R. L., Kennedy, C. and Kety, S. S.: The Effect of Mental Arithmetic on Cerebral Circulation and Metabolism. J. Clin. Invest. **34:** 1101 (July), 1955.

In this study of cerebral metabolism in 13 university students and faculty members, the effects of mental exertion (solving arithmetic problems) were examined. Some changes were found in the electroencephalographic pattern, in the pulse rate and in the mean arterial blood pressure. However, no changes were seen in cerebral blood flow, oxygen consumption, or vascular resistance during the processes of thought and reason. Neither were there changes in oxygen, CO_2, pH or hemoglobin of blood.

This lack of correlation between mental activity and measurable physiologic variables suggests that the brain utilizes by far the greater part of its energy requirements merely in keeping itself functioning. The presence of "useful work" adds only a minute amount to the total load. Or the brain may be considered as a group of functional units, reciprocally related so that increased activity in one group results in decreased activity in another. No measurable differences would then be detected in the overall metabolic activity. Other mechanisms may also be in effect.

WAIFE

Horner, W. H., Hecker, A. R., Moegrath, B. G. and Ritchie, H. D.: The Action of Adrenalin, l-Noradrenaline, Acetylcholine and Other Substances on the Blood Vessels of the Perfused Canine Liver. J. Physiol. **128:** (June 28), 1955.

This paper records the effects of certain physiologically active substances on the circulation within the canine liver.

Hepatic venous outflow was measured by means of a modified Gaddum outflow recorder and liver volume was measured by total plethysmography and the method of Andrews (1932). Homologous heparinized blood, diluted with 3 per cent PVP in Ringer Locke Solution, was the perfusion fluid. Portal venous inflow was supplied from a constant level reservoir.

Adrenalin and *l*-noradrenalin into the hepatic artery reduced portal venous inflow, hepatic artery flow and either increased or decreased hepatic venous outflow and liver volume. These drugs injected into the portal vein reduced portal venous inflow, hepatic venous outflow and liver volume. Depending on the dose, adrenalin and noradrenalin, injected into the hepatic vein, produced variable response in all parameters. Adrenalin and noradrenalin produced constriction of the hepatic artery and portal vein, but neither dilatation nor constriction of the hepatic venous tree.

Acetylcholine dilated the hepatic artery only if it was constricted. It constricted the hepatic vein and occasionally the portal vein. Acetyl B methylcholine and carbaminoyl chloride produced the same results as acetylcholine, except that the drug was equally active when injected into either the hepatic artery or the portal vein. Histamin dilated the hepatic artery if it was constricted, and constricted the hepatic vein.

Adrenalin injected into the hepatic artery before acetylcholine prevented the constriction of the hepatic vein. If adrenalin is injected after acetylcholine, the actions of acetylcholine occur and then those of adrenalin.

WECHSLER

Schottstaedt, W. W., Grace, W. J. and Wolff, H. G.: Life Situation, Behavior Patterns, and Renal Excretion of Fluid and Electrolytes. J.A.M.A. **157:** 1485 (Apr. 23), 1955.

About 400 observations were made on 5 subjects re the rates of renal excretion of water, sodium, potassium and creatinine during situations evoking a variety of adaptive patterns, including altered behavior and expressed attitudes, emotions and feelings. Observations were made under circumstances of ordinary daily work with no specific restrictions applied either in food or fluid intake, or in the amount of intensity of muscular activity. When in response to situations, persons were prepared for short violent action, as for fight or flight, or during situations evoking aggressive behavior, attitudes or feelings of excitement, intense anger and apprehension, sodium and water loss occurred. Reactions featured by listless behavior, reduction in activity, attitudes of despair and depression were associated with retention of fluid and electrolytes. Such retention of fluid and electrolytes accompanied responses of fright and reactions to severe noxious stimulation or pain. In persons faced with threatening situations eliciting restless behavior, alertness, readiness for action, with mixed feelings of confidence, uneasiness and tension, renal excretion of water and sodium was decreased and body weight was increased. In similar situations featured by unusual constraint, retention of potassium might occur as well. Diuresis of water and salt with resultant weight loss occurred with endings of such periods of threat. The adaptive value

of these mechanisms is evident for the basic needs of food getting, self-preservation and procreation; however, when they are evoked as reactions to threatening symbols or sustained interpersonal and social pressures, they serve no useful purpose. Persons with marginal circulatory and renal efficiency, who have excess fluid accumulation, may be decompensated by the retention of additional fluid. The evaluation of any investigative procedures involving fluid and electrolytes should include an appraisal of the person's setting and his reactions to the setting.

KITCHELL

RHEUMATIC FEVER

Weinstein, L., Boyer, N. and Goldfield, M.: Rheumatic Heart Disease in Scarlet-Fever Patients Treated with Penicillin. A Follow-up Study after Seven Years. New England J. Med. **253:** 1 (July 7), 1955.

In 1946, a group of 167 patients with scarlet fever were treated with intramuscular penicillin for 10 days. Twelve of these patients were believed to have developed acute rheumatic fever despite the penicillin. The evidence for this diagnosis in 10 patients consisted largely of changes in the PR and QTc intervals. The current study was designed to examine these same patients seven years after they had penicillin treatment for scarlet fever. Of the original 167, 110 patients returned for study after the seven-year interval. Of the 100 patients who were not considered to have rheumatic fever in 1946, none had detectable heart disease. Of 10 patients suspected of having rheumatic fever in 1946, 4 had mitral insufficiency and stenosis and 2 had had involvement of both the aortic and mitral valves. Two other patients, who had abnormal electrocardiograms in 1946, were classified as having probable rheumatic heart disease in 1953 on the basis of apical systolic murmurs and alterations in the configuration of the heart.

The data are considered to suggest that treatment of acute streptococcal pharyngitis in children with penicillin does not suppress appreciably the development of rheumatic heart disease. Such penicillin therapy is also felt to so alter the usual clinical features of acute rheumatic fever that carditis, as manifested largely by the electrocardiographic changes, becomes the outstanding feature. This study differs sharply from other reports, and the authors feel this may be explained by the younger age and greater susceptibility of the patients dealt with in this study. The demonstration of prolongation of the PR or QT interval or both is felt to be of greater significance than other abnormalities in suspected rheumatic carditis, and minor T wave changes are of little or no importance because they may be related to fever or tachycardia or both. It is suggested that prolonged conduction in the electrocardiograms may merit reconsideration as one of the "major" criteria for the diagnosis of rheumatic carditis in patients with proven streptococcal infections.

ROSENBAUM

Goodale, F., Jr., Sanchez, G., Friedlich, A. L., Scannell, J. G. and Myers, G. S.: Correlation of Pulmonary Arteriolar Resistance with Pulmonary Vascular Changes in Patients with Mitral Stenosis before and after Valvulotomy. New England J. Med. **252:** 979–983 (June 9), 1955.

The study was concerned with the correlation of pathologic changes found in lung biopsies with cardiac catheterization in 50 patients with mitral stenosis, subjected to mitral valve surgery. Cardiac catheterization data were obtained prior to operation in all patients, and on 16 of them, 5 to 28 months after operation. A few patients showed normal small pulmonary vessels, whereas the remainder showed varying degrees of fibrous intimal thickening. Medial hypertrophy in the small pulmonary arteries was not found in this material. There was no good correlation between the pulmonary arteriolar resistance and large vessel changes, hemosiderosis, the presence or absence of atrial Aschoff bodies, pulmonary capillary pressure, mitral valve area, arterial oxygen saturation, age of patient or duration of symptoms. Postoperative studies indicated that marked elevation of the pulmonary arteriolar resistance is reversible despite marked pathologic changes in small pulmonary vessels or alveolar walls if an adequate valvulotomy is done. The lack of correlation between the level of pulmonary arteriolar resistance and the magnitude of pathologic changes in the lungs is felt to suggest that vasoconstriction within the lungs is an important factor in the production of pulmonary hypertension in mitral stenosis. The fact that there was agreement, between biopsies and more detailed autopsy studies of the lung in four cases that died after surgery, is considered a sign that lung biopsies are representative of the lung as a whole as far as this study was concerned.

ROSENBAUM

Mohler, D. N., Wallin, D. G. and Dreyfus, E. G.: Studies in the Home Treatment of Streptococcal Disease. I. Failure of Patients to take Penicillin by Mouth as Prescribed. New England J. Med. **252:** 1116 (June 30), 1955.

A study was made of 245 patients with acute pharyngitis or otitis media due to the β-hemolytic streptococcus, and treated on the Home Medical Service of the Massachusetts Memorial Hospitals. The patients were supposed to take a tablet of 200,000 units of potassium penicillin G, 3 times daily by mouth for 7 days; 84 patients, or 34.3 per cent, admitted taking less than the prescribed amounts when subsequently reviewed while 56 per cent of these patients took the drug for less than 5 days. The reasons for taking less than the prescribed amount of drug were that the patient felt well after 1 or 2 days of therapy, carelessness, insufficient money to buy the full number of tablets, refusal of young children to take the medicine or misunderstanding the physician's instructions. The performance of patients receiving medication without charg

did not differ significantly from that of the rest of the group. This study is felt to represent a serious problem in the use of oral penicillin in the treatment of the ambulatory patient with streptococcal disease and the prophylaxis of rheumatic fever.

ROSENBAUM

Stolzer, B. L., Houser, H. B. and Clark, E. J.: Therapeutic Agents in Rheumatic Carditis. Arch. Int. Med. **95:** 677 (May), 1955.

The comparative effects of acetylsalicylic acid, cortisone and corticotropin on rheumatic carditis, as evidenced by the presence of murmurs during a 14-month period of observation, were observed in 52 patients treated with acetylsalicylic acid, 38 patients treated with cortisone and 38 patients treated with corticotropin.

The fewest patients with significant murmurs at 14 months occurred in the cortisone-treated group; 18 per cent, in contrast to 34 per cent in those patients treated with either acetylsalicylic acid or corticotropin. It seemed that cortisone prevented the appearance of apical systolic murmurs and caused the disappearance of existing apical systolic murmurs during the treatment period to a greater degree than either acetylsalicylic acid or corticotropin. This difference during therapy was reflected at the 14th-month evaluation. The seemingly favorable effect of cortisone was also evident when aortic diastolic and apical mid-diastolic murmurs were considered, although the numbers were small.

The differences observed among the three treatment groups do not allow a definite conclusion as to whether cortisone and corticotropin are superior to acetylsalicylic acid in the prevention of rheumatic valvular heart damage.

BERNSTEIN

Van Leeuwen, G. J., Kelly, H. G. and Jackson, R. L.: Corticotropin and Cortisone in Rheumatic Fever. Am. J. Dis. Child. **89:** 304 (March), 1955.

These studies were aimed at determining whether treatment with cortisone or corticotropin (ACTH) altered the abnormal electrophoretic patterns of the serum proteins characteristically found in acute rheumatic fever. Serial electrophoretic analyses of the protein of 24 plasma or serum samples of nine children with definite acute rheumatic fever were performed. All of these patients were treated with either 1 to 1.5 mg. ACTH per pound of body weight per day or 200 to 300 mg. per day of cortisone. The dosage was decreased gradually and discontinued in 1 to 10 weeks. Serum mucoproteins and erythrocyte sedimentation rates were also reported and comments made on the course of the disease.

These preliminary data indicated that hormonal therapy exerted a definite effect on albumin, α-globulin, β-globulin and γ-globulin. The rapid return of percentage albumin to normal from subnormal levels was interpreted as a compensatory response, resulting from the concomitant decrease in the percentage of globulins.

Alpha-globulin decreased to normal more rapidly than in the nonspecifically treated control group. This may mean that the acute-phase reactions in rheumatic fever are shortened by hormonal therapy. Beta globulin either remained elevated or became more elevated during the course of treatment. Gamma globulin decreased rapidly, sometimes to subnormal levels. This suggested that the major effect of the hormones was related to hypersensitivity processes of the disease. Hormonal therapy had little effect on the α_2-globulin or mucoprotein tyrosine. These findings made the authors skeptical of the value of these drugs in preventing residual cardiac damage.

MAXWELL

ROENTGENOLOGY

Job, J. M., Ilha, D. O., Pastous, P. S. and Campos, F. D.: Dextrocardial and Unsuspected Absence of the Right Pulmonary Artery in An Adult Demonstrated by Angiocardiography. Am. J. Roentgenol. **73:** 950 (June), 1955.

The authors report a case of absence of the right pulmonary artery demonstrated by angiocardiography in an otherwise healthy adult male. The right-sided bronchi were reduced in caliber. The heart was drawn over into the right chest with a shift of the heart and mediastinum towards the right in expiration and back towards the left on inspiration.

SCHWEDEL

McKusick, V. A. and Cooley, R. N.: Drainage of Right Pulmonary Vein into Inferior Vena Cava. Report of a Case with a Radiologic Analysis of the Principal Types of Anomalous Venous Return from the Lung. New England J. Med. **252:** 291 (Feb. 24), 1955.

A woman aged 26 years, with anomalous drainage of the right pulmonary vein into the inferior vena cava, diagnosed by means of angiocardiography is described. It is said that this diagnosis has been reported during life in 13 other instances. This anomaly is compatible with life and, theoretically, the surgical removal of the lung with normal venous drainage in these patients would be disastrous. Associated cardiac anomalies were apparently absent in the cases diagnosed during life. The hemodynamic abnormality in this lesion is similar to that of an interatrial septal defect and to a lesser degree that of an interventricular septal defect. However, momentary or partial reversal of the shunt is anatomically impossible in this lesion. There may be partial or total drainage of pulmonary venous blood to the right side of the heart. If there is total venous transposition, there must be some compensatory defect, usually an interatrial septal defect, and such patients are usually mildly or intermittently cyanotic. The right ventricular workload is increased and this

chamber usually dilates and hypertrophies. The pressure is usually normal in the right atrium, right ventricle or pulmonary artery, the right atrium dilates and the left atrium tends to grow smaller. Relative pulmonic stenosis, that is, a systolic murmur at the left sternal border with a drop in systolic pressure across the pulmonic valve without anatomic pulmonic stenosis, has been reported in this condition. This condition may be associated with other anomalies which may be benefited or made worse as a result. The radiologic features include increased vascularization of the lung fields and "hilar dance," dilatation of the right atrium, increase in size of the right ventricular, dilatation of the superior vena cava if part of the anomalous venous return, anomalous vascular patterns in the lungs in some cases, and in some cases outpouching of the superior vena cava where the anomalous vein returns, changes in the upper mediastinum for dilatation of the normal right superior vena cava or from dilatation or persistence of a left superior vena cava. Angiocardiography is especially helpful in the diagnosis of these lesions, and the anomalous veins can usually be demonstrated and recirculation of the right side of the heart with continuous opacification can usually be seen.

The authors have developed a classification of the individual types of anomalous pulmonary venous drainage based upon a careful study of 20 cases:

A. Partial Transposition
   1. To Inferior Vena Cava
   2. To Superior Vena Cava
      a. Right Superior Pulmonary Vein
      b. Left Superior Pulmonary Vein
   3. To Right Atrium Directly
   4. Left Pulmonary Vein (s) to Right Atrium via Persistent Superior Vena Cava on Left and Coronary Sinus

B. Total Transposition
   1. To Right Atrium (point of entry unspecified)
   2. To Right Atrium via Coronary Sinus
   3. Persistent Left Superior Vena Cava to Superior Vena Cava on the Right ("Figure-of-Eight Syndrome")
   4. To Superior Vena Cava on Right via Azygos Vein

It is felt that in retrospect this type of malformation could have been suspected from the routine radiogram of the chest in 11 cases and the diagnosis suggested or established by angiocardiography in 5 additional ones.

ROSENBAUM

Barnes, B. A., Shaw, R. S., Leaf, A. and Linton, R. R.: Oliguria Following Diagnostic Translumbar Aortography: Report of a Case. New England J. Med. **252:** 1113 (June 30), 1955.

It is pointed out that, in general, abdominal aortography has not been attended by any significant mortality or morbidity, although there may be such complications as acute iodism, extravasation of the contrast medium, hematoma development, direct injection of secondary arterial branches with subsequent injury to the organ supplied and extension of an arterial thrombosis. The authors report a case of a man aged 57 years who had a thrombosis of the abdominal aorta and who developed prolonged oliguria following diagnostic translumbar aortography with iodopyracet (Diodrast). An aortogram had been done four months earlier at another hospital. It was believed that the complete block of the abdominal aorta caused both kidneys to be perfused with a high concentration of the iodopyracet. This may have resulted in renal parenchymal injury or there may have been an allergic reaction following the previous exposure to an iodinated compound. The authors review four other instances from the literature of renal damage following the use of radiopaque materials. The patient reported made a satisfactory recovery following treatment in the accepted fashion with careful limitation of fluid intake, a cation-exchange resin to promote potassium excretion in the stool and a diet regulated to decrease tissue breakdown.

ROSENBAUM

Zuhdi, M. Z. and Lyons, H. A.: Angiocardiographic Study of a Case of Double Aortic Arch without Symptoms. Am. J. Med. **18:** 1022 (June), 1955.

A case of a complete, double aortic arch is presented. The patient had no symptoms or signs referable to the anomaly. Attention is called to the importance of angiocardiography in the differential diagnosis of mediastinal masses and for clear delineation of a double aortic arch.

HARRIS

SURGERY AND CARDIOVASCULAR DISEASE

Goldberg, H. and Downing, D. F.: The Physiological and Clinical Changes Following Closure of Atrial Septal Defects by Atrio-Septo-Pexy. Am. Heart J. **49:** 862 (June), 1955.

Physiologic and clinical data are presented in a group of 15 patients in whom follow-up hemodynamic studies were obtained following closure of the atrial septal defect. Atrioseptopexy was performed in 13 patients. One of these had a mitral commissurotomy as well. In two patients, surgical correction was made of the anomalous pulmonary venous drainage, as well as of the atrial septal defect. The hemodynamic studies revealed complete elimination of the left-to-right shunt in 12 cases. In two patients the shunt was decreased and there was no change in one.

RINZLER

Haight, C. and Sloan, H.: Successful Cardiac Resuscitation despite Perforation of the Heart during Massage. Ann. Surg. **141:** 240 (Feb.), 1955.

The authors reported a case of asystole of the heart during an operation which was treated with

manual massage, successful resuscitation occurring after 3 hours and 15 minutes of this procedure. In the process, perforation of a previously infarcted area was produced, which was controlled by suturing the laceration.

Following recovery from the operation, the patient showed no evidence of cerebral damage, despite the duration of cardiac arrest. However, about seven weeks postoperatively he suddenly died after experiencing acute precordial pain for several minutes. Postmortem examination revealed organizing emboli and thrombi in several small pulmonary arteries and multiple hemorrhagic infarcts in both lungs.

ABRAMSON

Lam, P. T. C., Wrzesinski, J. T., and Walske, B. R.: Cardiac Arrest. Am. J. Surg. **89:** 593 (Mar.), 1955.

The authors presented two cases of cardiac arrest occurring a short time after operation and suggested that prophylaxis was the best means of meeting the problem. The value of repeated doses of atropine to block as far as possible the trigger mechanism of a vagovagal reflex in an already sensitized heart was emphasized. Attention was also called to the fact that cardiac massage was a traumatic procedure and could lead to rupture of the right ventricle.

ABRAMSON

Glenn, W. W. L. and Turk, L. N., III: The Surgical Treatment of Mitral Insufficiency: The Fate of a Vascularized Transchamber Intracardiac Graft. Ann. Surg. **141:** 510 (April), 1955.

An experimental study was performed on 23 dogs in which a plug of tissue, composed mainly of blood vessels contained in an inverted autogenous vein segment, was passed into the chamber of the left ventricle, via the left atrium, and then out of the ventricle, to be fixed on the epicardial surface. The results indicated that viability of the graft and patency of the artery in the graft could be expected in the majority of the cases.

The work was performed with the possibility in mind that such a technic could be applied to the patient with mitral insufficiency.

ABRAMSON

Likoff, W., Berkowitz, D., Denton, C., Goldberg, H. and Reale, A.: Transventricular Commissurotomy in Aortic Stenosis. J.A.M.A. **157:** 1367 (Apr. 16), 1955.

This study analyzes the clinical experiences in a group of 79 patients who had an aortic commissurotomy alone. There were 65 males and 14 females ranging in age from 14 to 67 years. The three groups consisted of group 1 (33 patients) in whom aortic stenosis was the only valvular lesion; group 2 (36 patients) in whom aortic stenosis was combined with other valvular lesions which were physiologically insignificant; group 3 (10 patients) in whom aortic stenosis was associated with valvular lesions other than mitral stenosis, at least one of which was physiologically significant and was not corrected at the time of surgery. In group 2, 32 patients had aortic insufficiency as the only other involvement. In seven patients of group 3, aortic insufficiency was the only other involvement. Immediate mortality rates in group 1 were 18.1 per cent, in group 2, 18.7 per cent and in group 3, 71.4 per cent. All of these patients subjected to operation had had previous medical treatment. The average medical therapy had extended over 4.6 years and digitalis, or an allied product, had been prescribed for an average of 3.8 years. In this series it was repeatedly demonstrated that once symptoms developed in aortic stenosis, they never abated completely under an unrestricted routine. Only the speed of deterioration was unpredictable.

Forty-four patients surviving surgery were surveyed over a period of 3 to 24 months following operation. Two of these died, leaving 42 survivors at the time the paper was written. All of the 42 patients had experienced fatigue as a major operative symptom and 36 of them were significantly improved after operation. Thirty-seven patients had had dyspnea and 33 were improved after operation; 7 no longer experienced the complaint at all. Nineteen of the patients had complained of significant angina preoperatively; 18 of these were markedly improved and 6 no longer had the complaint. In screening the entire 79 cases, it appears that operative mortality is increased in the presence of significant aortic regurgitation, age over 50 years, poor functional status and angina. The mortality in aortic commissurotomy for pure stenosis is at least three times as great as that in mitral commissurotomy. On the basis of these experiences, significant aortic regurgitation and congestive heart failure are absolute contraindications to this operation although additional insignificant valvular lesions are not deterrents.

Since this paper was written, further experiences to be reported later have demonstrated a transaortic approach to the aortic valve yields a better opening with a much lower mortality. This group now contains more than 50 patients with 5 deaths, and the transaortic approach has now replaced the presently described technique of transventricular approach.

KITCHELL

Dressler, W.: Idiopathic Recurrent Pericarditis. Comparison with the Postcommissurotomy Syndrome: Considerations of Etiology and Treatment. Am. J. Med. **18:** 591 (April), 1955.

Comparing 42 episodes of idiopathic pericarditis in 12 patients with 72 attacks of the postcommissurotomy syndrome in 24 patients, the author finds a striking resemblance between the clinical and laboratory features of each. Both diseases include pericarditis, pleurisy and pneumonitis. In some instances the occurrence of gallop rhythm, dilatation of the heart, transient atrial flutter-fibrillation and congestive heart failure suggest myocardial involvement. The outstanding clinical features are

pain of the pleuropericardial type and fever. Both syndromes usually have a benign course and tend to relapse frequently.

There are compelling reasons for the belief that the postcommissurotomy syndrome is a manifestation of rheumatic activity. The same etiology is suggested for some cases of "idiopathic" pericarditis by the following facts: (1) close resemblance of idiopathic pericarditis and the postcommissurotomy syndrome; (2) presence of major and minor rheumatic manifestations in a relatively large number of cases of idiopathic pericarditis reported in the literature and in two thirds of the cases observed by the writer; (3) salicylates and Pyramidon sometimes have a beneficial effect in cases of idiopathic pericarditis and (4) idiopathic pericarditis is predominantly a disease of the adult. Rheumatic fever in the adult is known to manifest itself often atypically, as a benign exudative process which may heal without residual heart disease. The findings of pleurisy and/or pneumonitis aid in the differentiation of idiopathic pericarditis from an acute coronary attack.

HARRIS

O'Donnell, J. A. and McDermott, T. F.: Anesthetic Problems of Surgical Correction of Aortic Insufficiency. Anesthesiology **16:** 342, (May), 1955.

In this presentation the authors summarize their mode of conduction of anesthesia for surgical procedures involving the insertion of a prosthetic aortic valve in patients with aortic insufficiency. The experiences during the anesthesia of forty-two patients, in whom the operation was performed for the amelioration of progressively increasing and medically irreversible congestive heart failure due to aortic insufficiency, form the basis of this report.

All patients are admitted one week prior to operation for complete cardiac work-up, evaluation, hospital acclimatization, intensive treatment of congestive failure and preoperative preparation with rest, sedation, and antibiotics. Barbituates, morphine and scopolamine are employed as premedication. Anesthesia is induced by topical endotracheal intubation, and maintained with light nitrous oxide and oxygen supplemented by small amounts of ether or intravenous opiates. These patients tolerate anesthesia very poorly and the maintenance of anesthesia is a delicate balance between an anesthesia level, which does not result in cardiovascular depression, but still provides adequate intrathoracic operating conditions. Continuous electrocardiographic tracings with direct visual use of the cathode-ray, oscilloscope and constant observation by a cardiologist during operation are advisable. Adequate preparations must be made to anticipate cardiovascular emergencies requiring either the rapid administration of blood to combat hemorrhage or the removal of blood in the event of extreme hypotension during occlusion of the aorta. Various cardiac medications and an electro-defibrillating machine should be available.

In this series three patients died while in the operating room. These patients were extremely and critically ill prior to operation, and their deaths were attributed primarily to underlying disease rather than to the anesthesia or surgery which were the immediate precipitating causes. In two other cases, death occurred within the first three postoperative days and anesthesia may have been a factor. Six other patients died at some subsequent date and these deaths were not related to anesthesia.

SAGALL

Elder, J. D., Nagano, S. M., Eastwood, D. W. and Harnazel, D.: Circulatory Changes Associated with Thiopental Anesthesia in Man. Anesthesiology **16:** 394, (May), 1955.

In order to study the circulatory changes associated with clinical thiopental anesthesia in man, cardiac output determinations were made on unselected hospital patients scheduled for barbiturate anesthesia. During the determinations, the patients also were being given nitrous oxide and oxygen according to the usual clinical use of thiopental anesthesia. The results in 14 patients are reported. After induction of anesthesia, the cardiac index (cardiac output in liters per minute divided by the surface area) fell in 12 cases, rose in 1 and was unchanged in the other as compared to values obtained during the sedated, control period. The average fall in cardiac index was about 20 per cent. The mean arterial blood pressure showed a fall in 11 patients, slight rise in 1 and was unchanged in 2. In 13 cases, the peripheral and central venous pressures showed a variable amount of fall with an average decline of 15 per cent of the initial determination. The overall resistance to the outflow of blood from the arterial tree showed a rise rather than a fall with decreasing cardiac output. The authors believe that the decrease in cardiac output observed under thiopental anesthesia arises from either a direct depressant effect of the drug on the heart or to venous pooling, with a resulting diminution in cardiac-filling pressure.

SAGALL

BOOK REVIEWS

Clues In The Diagnosis And Treatment of Heart Disease. *Paul D. White*, Springfield, 1955, Charles C Thomas, 174 pages, illustrations. $5.50.

The major purpose of this small book (170 text pages) is stated in the preface: it is to discuss briefly the diagnostic, prognostic and therapeutic clues, often omitted from current texts, which experience has shown to be of value. Because of the author's unrivalled experience in the field of heart disease, one would expect his discussion to be authoritative and comprehensive without reference to the observations of others. But he asked for suggestions from a small fraction of his almost innumerable friends throughout the world, and acknowledges the contributions of almost 100 of these in a list that is a veritable "WHO'S WHO" in cardiology.

The clues relate to the history, physical signs, roentgenology, electrocardiography and therapy. Many of them might be designated as of great negative value; for example, nine features of chest pain are listed which are helpful in *excluding* a diagnosis of angina. Virtually every symptom or physical sign that may be encountered in patients suspected of having heart disease is evaluated with wisdom and authority.

More than 30 pages are devoted to x-rays of the heart and great vessels. The films must have been chosen with great care, for they illustrate very beautifully the conditions which they identify. In the few pages on electrocardiography, major attention is properly given to such matters as axis deviation in normal hearts, acute and chronic cor pulmonale, myocardial infarction, pericarditis and myxedema. Here, too, the illustrations are beyond criticism.

The chapter on treatment is of the same high quality as those on diagnosis. Many wise suggestions are offered upon the recognition and prompt therapy of acute and chronic heart failure. It is hoped that in future editions the author will add a brief discussion of the more rapidly excreted forms of digitalis.

Inasmuch as there are few, if any, cardiologists in the world who have had Dr. White's intensive and world-wide experience in observation, discussion, teaching and writing, it would be hazardous to disagree with him or even to state an experience contrary to his. Having the protection of his warm friendship, I shall be so bold as to disagree with his statement (p. 58) that digitalis does not cause hallucinations or psychoses, inasmuch as I have encountered at least three instances of such disturbances caused repeatedly by this drug, even in the absence of heart failure. My own experiences with Mecholyl and Pronestyl in the treatment of paroxysmal tachycardia have obviously been less satisfactory than his.

It would be difficult to speak too highly of this small volume. Even those who specialize in cardiology can learn much from it, and it should be of enormous interest and value to those whose interests extend to a wider field of medicine. It was my great privilege to begin my study of heart disease with Dr. White more than 30 years ago, and I have continued to learn from him ever since. In that respect, I am one of the thousands who gratefully acknowledge his faithful and stimulating leadership.

H. M. MARVIN, M.D.

Cardiac Emergencies and Heart Failure—Prevention and Treatment. *Arthur M. Master, Marvin Moser and Harry L. Jaffe.* Philadelphia, Lea & Febiger, 1955. 203 pages, 14 figures. $3.75.

Although many will take exception to the authors' opinion that Digoxin is superior to whole digitalis leaf for routine use, this small book is excellent review reading for the internist and general practitioner. The management of cardiac arrhythmias, acute left ventricular failure and congestive heart failure is summarized in a clear and concise manner, and there are good chapters on coronary heart disease, syncope and dissecting aneurysm of the aorta. The writing, however, lacks clarity at times. For instance, a sentence concerning the effectiveness of nitroglycerin in angina pectoris might be interpreted to mean the drug helps only 10 per cent of patients. The discussion of the mechanism and treatment of cardiogenic shock also is somewhat confusing. It is difficult to understand why, if severe generalized vasoconstriction is present in this condition, vasopressor drugs should prove as beneficial as they do.

In the chapter on rheumatic fever and rheumatic heart disease, the therapeutic use of ACTH and cortisone is evaluated and the indications for mitral valve commissurotomy are summarized. A mortality rate of "less than 15 per cent" from the latter operation appears, however, to be too pessimistic. The management of hypertensive encephalopathy is well presented, and the chapter on traumatic heart disease emphasizes helpful criteria for diagnosis. The concluding chapter deals in a practical manner with cardiac complications encountered during surgical operations. There is an excellent bibliography and a detailed index, both of which add considerably to the value of the volume.

Transactions of The American College of Cardiology, Vol. IV, 1954. *Simon Dack, and Buno Kisch, eds.* New York, American College of Cardiology, 1955. 319 Pages.

Volume IV of the *Transactions of the American*

College of Cardiology contains the papers read at the convention of May, 1954 and the interim session of November, 1954. The sessions were symposia on *Prognosis in Heart Disease* and *Diet in Heart Disease*. The membership list and the constitution of the organization are also included.

In a preconvention meeting, Kedzi and Hilker showed that in hypertension there are degenerative changes in the sinoaortic reflex pathways and Dr. Theis recommended a low caloric diet as the best treatment for arteriosclerotic peripheral vascular disease, whereas Abramson pointed out the limited value of sympathectomy in these cases.

To start the symposium, David Scherf presented, the causes of sudden death and Freeman succinctly outlined the chemical changes associated with heart failure.

Smith and Priest followed their original 34 cases of subacute bacterial endocarditis and found that the severity of the underlying disease seems to be the important factor in longevity. The prognosis of acute myocarditis was discussed by Luisada.

Arbeit, Dolan and Stollerman found a direct relationship between the incidence of ballistocardiographic abnormality and severity of rheumatic activity. Dack and Robbin reviewed the problem of atherosclerosis and concluded that the condition may be controlled by the judicious application of the knowledge which we now have. The prognosis of the paroxysmal tachycardias is much better, according to Bishop, because of the newer drugs.

Russek and Zohman again emphasized that the mortality rate in "good risk" patients with myocardial infarction is 3.4 per cent, whereas in "poor risk" patients it is 60 per cent. Siegfried Salomon took immediate issue with them and concluded his paper on *The Good Risk in Myocardial Infarction* by stating that "prognostication in this disorder is, at best, educated guess work."

Gorelic followed 100 cases of coronary insufficiency and 50 with rheumatic valvular heart disease who had cardiopericardiopexy. In the coronary group the immediate mortality rate was 5 per cent, 10 per cent died during the postoperative follow-up period and the rest were all markedly improved. In the rheumatic group the operative mortality rate was 12 per cent. The rest showed excellent to good results with marked improvement in their heart failure. G. S. Blount Jr. discussed the improved prognosis in congenital heart disease in the past 15 years. Beck and Leighninger reviewed the experimental work, the rationale, the physiologic benefits and the statistical results of the Beck I and II operations and attempted to give them their proper place in the therapy of coronary artery disease. Brofman presents the indications and contraindications for the Beck operations as well as a follow-up of 20 patients who had the Beck I operation with 80 per cent improvement.

The symposium on *Diet* started with Rodahl who reported on atherosclerosis in the Eskimo without definite conclusion. Gofman reviewed the present status of the relationship of disturbance in blood lipid transport with the evolution of clinical coronary heart disease, presenting much of his own work plus some of the newer ideas in the field. The therapy of hypertension was reviewed by Jeffers.

A panel discussion of diet in arteriosclerosis and coronary heart disease by Dack, Bishop, Gofman, Jellinek, Nelson, Nichol, Rogers and Rodahl presented many interesting and stimulating points of view. The symposium on diet in hypertension, hypertensive heart disease and rheumatic fever was participated in by Harrell, Barrera Canedo, Edwards, Evans, Jeffers, Rodahl, Meneely and Wallis. This symposium contains many interesting and exciting comments and is very well worth reading.

The final panel discussion was one on diet in congestive heart failure and heart disease due to vitamin deficiency. The participants were Moseley, Barrera Canedo, Danowski, Evans, Jellinek, Meneely and Shuman. Of necessity, there was not much new in this discussion. However, some of the philosophic comments of Dr. Meneely might very well be worth reading for their esoteric value.

On the whole these transactions once more present in a succinct fashion a review of the topics which they profess to discuss. Though some of the material has not been published elsewhere, most of it is of a review nature. To the reader who wishes a short summary of these subjects, they will be helpful. However, the lack of a cross index makes it difficult to look up any specific material. Some of the proof reading was haphazard in places though, on the whole, the volume is rather well done.

AMERICAN HEART ASSOCIATION, INC.

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AHA ANNOUNCES AWARDS TO 118 INVESTIGATORS

A total of 118 research investigatorships and fellowships have been announced by the Association for the fiscal period beginning July 1, 1956 and continuing through June 30, 1957. The awards represent an expenditure of $847,000.

Included are 3 career investigatorships, 46 continued and renewed established investigatorships, 17 new established investigatorships, 20 continued and renewed research fellowships and 32 new research fellowships. The $847,000 awarded in these categories represents an increase from $695,000 awarded in the same categories last year. Still to be awarded are grants-in-aid for research projects. Last year 149 such grants were awarded.

The latest awards bring to more than $14-million the total monies allocated for research support by the Association since it was reorganized as a voluntary health agency in 1948. A complete list of award winners appears at the end of this section.

MAY 15 IS ABSTRACTS DEADLINE FOR 1956 AHA SCIENTIFIC SESSIONS

May 15 is the deadline for submitting abstracts of papers for presentation at the 1956 Annual Meeting and Scientific Sessions of the Association to be held in Cincinnati, October 27–31. It is also the deadline for applying for space to present scientific exhibits at the sessions.

The Scientific Sessions will be conducted October 27, 28 and 29 at the Cincinnati Music Hall. The use of this large public auditorium will enable the Association to provide greatly expanded space for exhibits—both scientific and technical.

To be accepted for presentation, papers must be based on original investigations in or related to the cardiovascular field. Abstracts should not exceed 300 words in length. They should be submitted in triplicate on special forms provided by the Medical Director of the Association. Applications for scientific exhibit space may also be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10.

PLAN REHABILITATION PROGRAMS AT REGIONAL WORKSHOPS

A major effort to focus professional and lay attention on the problems of rehabilitation of cardiacs will be undertaken by the Association in the next few months. The effort will have the cooperation of several governmental agencies with interest in the rehabilitation field.

An important part of the Association effort will be a series of five three-day regional workshops which will bring together members of various professional disciplines, as well as personnel of national, state and local heart associations and representatives of the cooperating agencies. This last category includes the Office of Vocational Rehabilitation, the Childrens' Bureau, the Bureau of Employment Security of the Department of Labor and the Extension Service of the Department of Agriculture.

Each workshop will be attended by 50 or 60 persons. Adequate medical representation at the workshops is considered to be of paramount importance to their success, as is the exploration of ways and means for mutual cooperation between the public agencies and Heart Associations in order to bring about increased rehabilitation service to persons with cardiovascular disease problems.

The schedule for the regional workshops:

April 11–13—Excelsior Springs, Mo.; April 17–19—Boyes Springs, Calif.; May 1–3—Augusta, Ga.; May 15–17—Lakeville, Conn.; May 22–24—Cleveland, Ohio.

BLAKESLEE AWARDS ENTRIES DUE BY TUESDAY, MAY 1

Newspaper and magazine articles, books, radio and television programs and films which were published or produced between March 1, 1955 and March 1 of this year will be eligible for the 1956 Howard W. Blakeslee Awards

competition of the American Heart Association. Entries must be submitted on special forms by May 1.

Blakeslee awards are given annually for efforts in any media of mass communication which in the opinion of the Association's Awards Committee contribute most to public understanding of the cardiovascular system and its diseases. The awards were inaugurated in 1952 to honor the memory and achievements of the late science editor of the Associated Press and founder of the National Association of Science Writers. They carry a minimum honorarium of $500 each.

Last year's awards, which were presented at the AHA Annual Meeting in New Orleans, were presented to Mrs. Frances Burns, medical writer for the Boston Daily Globe, Miss Jane Stafford, medical writer for Science Service, William Peters, magazine writer, and the Columbia Broadcasting System.

Additional information and entry blanks may be obtained from the American Heart Association, 44 East 23 Street, New York 10.

PAMPHLETS GIVE INFORMATION ON CORONARY OCCLUSION

Revision of the Association's pamphlet, "Heart Disease Caused by Coronary Atherosclerosis," has been completed by Paul D. White, M.D., and the new edition is now available to the lay public.

The pamphlet is particularly designed as a piece which the physician may give to his coronary artery disease patient who is interested in understanding the physiologic and pathologic phenomena underlying the condition. A new section on "What the Doctor Tells His Patient" has been included for this purpose.

Dr. White presents a complete but simple explanation of the mechanism of coronary occlusion and of the atherosclerotic processes which precede it. The pamphlet also contains an explanation of the anginal syndrome. Dr. White stresses the importance of having the patient and his family understand the background of coronary thrombosis as an aid to therapy and rehabilitation.

The Association has also issued a more general educational piece on coronary thrombosis intended for those whose interest in the subject is not likely to be as intense as that of the coronary patient. It is a four-page illustrated leaflet entitled "Heart Attack." This leaflet features a section on "What to Do in Case of a Heart Attack." "Heart Attack" is suitable for high school and college students, club groups and many patients.

Copies of both "Heart Disease Caused by Coronary Atherosclerosis" and "Heart Attack" may be obtained from your local Heart Association or the American Heart Association, 44 East 23 Street, New York 10.

THREE CARDIAC CLINICS NOW AVAILABLE

Three titles in the Association's audio-visual educational series for physicians, Cardiac Clinics, are now available in both kit and album form. These are:

"The Role of the P-A Film of the Chest in Cardiology"—Cardiac Clinic No. 1, prepared by William R. Christensen, M.D., Professor of Radiology at the University of Utah College of Medicine. Consists of two 12 inch, 33⅓ rpm records with a running time of approximately 35 minutes, 39 correlated slides and script.

"Prevention of Rheumatic Fever"—Cardiac Clinic No. 2 prepared by Gene H. St ollerman, M.D., Assistant Professor of Medicine, Northwestern University Medical School. Consists of three 12 inch, 33⅓ rpm records with a running time of 44 minutes, 31 correlated slides and script.

"Functional Pathology of Occlusive Coronary Disease"—Cardiac Clinic No. 3 prepared by Jesse E. Edwards, M.D., Professor of Pathologic Anatomy, Mayo Clinic and Mayo Foundation. Consists of two 12 inch, 33⅓ rpm records with a running time of 26 minutes, 28 correlated slides and script.

Each of these Cardiac Clinics is available in two forms, kit or album. The kit includes the records, slides and slide box, script and table-top viewer in a special wooden case. Its cost is $150 plus shipping charges. The album is designed for those who own one kit and want to add new subjects to their Cardiac Clinic

library. It includes the record, slides and script and may be obtained for $40 with express charges prepaid. Kits may also be rented at a cost of $5 for three days plus railway express charges both ways. Additional copies of the scripts may be obtained for either kits or albums at a cost of $6 per hundred with a minimum order of 25 copies required.

To purchase, order from the American Heart Association, 44 East 23 Street, New York 10. To rent the kits, order from the American Heart Association Film Library, 13 East 37 Street, New York 16.

PROFESSIONAL LITERATURE AVAILABLE THROUGH AHA

Among the professional publications available from the Association are the "Atlas of Congenital Cardiac Disease" by Maude E. Abbott, M.D., and "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels."

The Atlas is the classic monograph, first published in 1936 and long out of print, which was reissued by the Association exactly as it appeared in its original edition. Since its reprinting, more than 1,700 copies have been ordered. Its cost is $5.00.

Nomenclature is a revised and expanded edition prepared by the Criteria Committee of the New York Heart Association and published by the American Heart Association. The 359-page volume is priced at $4.95.

Also available from the Association are the Proceedings of the Annual Meeting of the Council for High Blood Pressure Research for the years, 1952, 1953 and 1954. The three volumes may be obtained for a combined price of $4. The 1954 volume alone costs $2.50.

GUIDE FOR BLOOD VESSEL BANKS

Reprints of the guide, "Recommendations for the Establishment and Maintenance of a Blood Vessel Bank," originally published in the February, 1956 *Circulation*, are available from the Association.

The guide is designed to aid clinical investigators in the establishment of blood vessel banks under standard conditions and to encourage a "certain uniformity in the procurement and preservation of vascular grafts for evaluations." It was drawn up by a committee of the Scientific Council of the Association which included Jere W. Lord, Jr., M.D., New York; Robert E. Gross, M.D., Boston; Charles A. Hufnagel, M.D., Washington; and Abel A. Lazzarini, Jr., M.D., New York.

Copies of the guide may be obtained from the Medical Director, American Heart Association, 44 East 23 Street, New York 10.

MEETINGS CALENDAR

March 19–22: Eighth Annual Scientific Assembly of the American Academy of General Practice, Washington, D. C., Armory. Secretary, American Academy of General Practice, Broadway at 34th, Kansas City 11, Mo.

March 24–25: American Psychosomatic Society, Sheraton Plaza Hotel, Boston. Theodore Lidz, 33 Cedar St., New Haven 11.

April 3: Third Microcirculatory Conference, Hotel Schroeder, Milwaukee, Wisconsin. Dr. G. P. Fulton, Dept. of Biology, Boston University, 675 Commonwealth Ave., Boston 15.

April 4–6: American Association of Anatomists, Milwaukee. Normand L. Hoerr, 2109 Adelbert Rd., Cleveland 6.

April 9–12: 30th Annual Congress, International Anesthesia Research Society, Miami Beach. Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland 12.

April 11–13: American Surgical Association, White Sulphur Springs, W. Va. R. Kennedy Gilchrist, 59 E. Madison St., Chicago 3. .

April 15: American Society of Biological Chemists, Atlantic City. Philip Handler, Duke University, Durham, N. C.

April 15–16: American Society for Artificial Internal Organs, Atlantic City. Peter F. Salisbury, M.D., Institute for Medical Research, Cedars of Lebanon Hospital, 4751 Fountain Avenue, Los Angeles 29.

April 15–20: American Society for Pharmacology and Experimental Therapeutics, Atlantic City. C. C. Pfeiffer, Emory University School of Medicine, Emory University, Ga.

April 15–20: American College of Allergists, New York. F. W. Wittich, 401 Marquette Bank Bldg., Minneapolis 2.

April 15–21: American Society for Experimental Pathology, Atlantic City. Cyrus C. Erickson, 874 Union Ave., Memphis 3.

April 26–28: American Association of Pathologists and Bacteriologists, Cincinnati. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29.

April 27–28: American Gastroenterological Association, Atlantic City. H. Marvin Pollard, University Hospital, Ann Arbor, Mich.

April 29: American Federation for Clinical Research,

Atlantic City. William W. Stead, V. A. Hospital, Minneapolis 17.

April 30: American Society for Clinical Investigation, Atlantic City. A. O. DeWeese, 515 East Main Street, Kent. O.

May 1–2: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11.

May 3–4: American Geriatrics Society, Malford W. Thewlis, 25 Mechanic Street, Wakefield, R. I.

May 6–11: Society for Pediatric Research, Buck Hill Falls, Pa. Sidney S. Gellis, 330 Brookline Ave., Boston 15.

May 29–June 3: Society of American Bacteriologists, Houston. J. H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

June 7–10: American Therapeutic Society, Chicago. O. B. Hunter Jr., 915 19 St. N. W., Washington, D. C.

June 7–10: American College of Chest Physicians, Chicago. Murray Kornfeld, 112 E. Chestnut St., Chicago 11.

June 10: Society for Vascular Surgery, Chicago. Henry Swan, 4200 East 9th Ave., Denver 7

June 8–12: American Medical Women's Association, Chicago. Lilliam T. Majally, 1790 Broadway, N. Y. 19.

June 18–20: American Neurological Association, Atlantic City. Charles Rupp, 133 South 36th Street, Philadelphia 4.

ABROAD

March 6–9: Ciba Foundation Symposium on Influence of I Ionizing Radiation on Cell Metabolism (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London W. 1.

March 22: The Biochemical Society, Annual General Meeting, London. Dr. F. L. Warren, Biochemistry Dept., The London Hospital Medical College, Turner St., London E. 1.

March 26–28: Ciba Foundation Symposium on the Biophysics and Biochemistry of Viruses (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London W. 1.

March 28–April 3: First International Congress of Analytical Chemistry, Rio de Janeiro. Secretary General, International Commission of Agricultural Industries, 18 Avenue de Villars, Paris 7e.

April 3–7: 6th Annual Conference on High Energy Nuclear Physics, sponsored by National Science Foundation and Atomic Energy Commission, Rochester, N. Y. Professor Arthur Roberts, Dept. of Physics, University of Rochester, Rochester, N. Y.

April 24–27: Annual Health Congress, Royal Sanitary Institute, Blackpool, England. P. Arthur Wells, Esq., Royal Sanitary Institute, 90 Buckingham Palace Rd., London S. W. 1.

April 28–May 5: Third International Conference on Health Education, Rome, Italy. Lucien Viborel, Secretary-General of Union, 92 rue Saint-Denis, Paris 1er, France.

May 9: 9th World Health Assembly, World Health Organization (WHO), Palais des Nations, Geneva, Switzerland.

May 24–26: First International Congress of Infectious Pathology, Lyon, France. Professeur Sedallian, President of Committee of Organization, 77 rue Pasteur, Lyon, France.

June 20–22: Ciba Foundation Colloquium on Endocrinology, Regulation and Mode of Action of Thyroid Hormone (by invitation), London. Dr. G. E. Wolstenholme, Director of Foundation, 41 Portland Place, London W. 1.

AHA AWARD WINNERS

Following is a complete list of career investigators, established investigators and research fellows selected for support during the fiscal year beginning July 1, 1956 by the Association's Research Committee.

Career Investigators

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Pappenheimer, John, Harvard Medical School, Boston.

Coons, Albert H., Harvard Medical School, Boston.

Continued Established Investigators

Abelmann, Walter H., circulation in disorders of metabolism and the regulatory role of the liver, Thorndike Memorial Laboratory, Boston City Hospital and Department of Medicine, Harvard Medical School, Boston.

Aikawa, Jerry Kazuo, immunophysiology, University of Colorado School of Medicine, Denver.

Barker, Earl Stephens, renal physiology, normal and pathologic, University of Pennsylvania, Renal Study Section, Philadelphia.

Beck, William Samson, mechanism by which hydrogen made available by carbohydrate oxidation is utilized for fatty acid synthesis, New York University College of Medicine, New York.

Briller, Stanley Arthur, energetics of the myocardium, New York University College of Medicine, New York.

Brodsky, William Aaron, renal and electrolyte metabolism, University of Louisville School of Medicine, Louisville.

Cavert, Henry Mead, metabolism and permeability of heart tissue investigated with isotopic techniques, University of Minnesota Medical School, Minneapolis.

Cohn, Mildred, mechanisms of phosphorylation and phosphate transfer reactions, Washington University School of Medicine, St. Louis.

Conn, Hadley L., Jr., study of alterations in pressure-volume-flow relationships within cardiovascular system produced by direct cardiovascular stresses; and effect of these alterations on transcapillary kinetics and organ metabolism, University of Pennsylvania Medical School, Philadelphia.

Curran, George Lally, metabolic aspects of cardiovascular disease with particular reference to lipid metabolism, University of Kansas Medical Center, Kansas City, Kan.

Drell, William, biochemical studies of the sympathetic nervous system in relation to cardiovascular function, University of California School of Medicine, San Francisco.

DuBois, Arthur Brooks, gas exchange in the lungs, mechanics of breathing and pulmonary capillary blood flow, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

Eckstein, Richard W., coronary collateral circulation and oxygen consumption of the right ventricle, Western Reserve University School of Medicine, Cleveland.

Edelman, Isidore Samuel, body water and electrolytes studied with tracers, University of California School of Medicine, San Francisco.

Elkinton, J. Russell, cardiovascular physiology, University of Pennsylvania School of Medicine, Philadelphia.

Farber, Saul J., role of electrolytes and their relationship to extracellular and intracellular organic constituents in heart disease and other diseases producing edema, New York University College of Medicine, New York.

Gaudino, Mario, intra and extra-cellular distribution of water and electrolytes in the organism as a whole and in tissues by means of radioactive indicators, New York University College of Medicine, New York.

Gergely, John, energetics and contractile proteins of heart muscle, Massachusetts General Hospital, Boston.

Goldthwait, David Atwater, biosynthesis of purine nucleotides, Western Reserve University School of Medicine, Cleveland.

Goodall, McChesney, effect of cervicostellate ganglionectomy on adrenaline and noradrenaline content of sheep heart; and unknown sympatholytic factor present in mammalian heart, Duke University Medical School, Durham, N. C.

Goodyer, Allan V. N., hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes, Yale University School of Medicine, New Haven, Conn.

Grisolia, Santiago, enzymatic patterns of nitrogen metabolism in heart muscle, University of Kansas Medical School, Kansas City, Kan.

Kaplan, Melvin, attempt to localize tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of fluorescein-labeling technique; possible application to study of pathogenesis of cardiac and skin lesions in rheumatic fever, House of the Good Samaritan and Children's Medical Center, Boston.

Lepeschkin, Eugene, electro-physiological interpretation of normal and pathological ventricular complex of the electrocardiogram, University of Vermont, Burlington.

Mackler, Bruce, metabolic sequences involved in electron transport in mammalian tissues, Institute for Enzyme Research, University of Wisconsin, Madison.

Mateer, Frank M., cardiovascular effects of specific electrolyte depletion and repletion studies by means of dialysis technique; and ballistocardiographic studies in the normal and abnormal subject, University of Pittsburgh School of Medicine, Pittsburgh.

Mathews, Martin B., physical chemistry of acid mucopolysaccharides of connective tissue and their protein complexes, University of Chicago, Chicago.

Merrill, John P., metabolic and electrolyte disorders in renal failure, Peter Bent Brigham Hospital, Boston.

Metcalfe, James, changes in the maternal circulation during pregnancy and labor, Boston Lying-in Hospital, Boston.

Mommaerts, Wilfried F. H. M., biochemistry of muscular contraction, Western Reserve University School of Medicine, Cleveland.

Osborn, John J., extra-corporeal circulation, physiology of hypothermia, and intra-cellular fluid and ionic shifts during respiratory acidosis, Stanford University School of Medicine, San Francisco.

Paterson, Philip Young, pathogenesis of selected forms of tissue damage, University of Virginia School of Medicine, Charlottesville.

Peterson, Lysle Henry, volume pressure, 'distensibility' of intact veins, arterial circulation with view to calculating stroke volume, integration of peripheral c-v reflexes, University of Pennsylvania Medical School, Philadelphia.

Plaut, Gerhard W. E., pathways and compounds of intermediary metabolism with particular regard to properties of heart muscle, New York University College of Medicine, New York.

Rose, John C., studies of circulation in dog using a mechanical left ventricle; sonic flowmeter; aortic insufficiency; and relationship between arterial pressure and cardiac auscultatory phenomena, Georgetown University Medical Center, Washington, D. C.

Sanadi, D. Rao, oxidative phosphorylation and amino acid metabolism, University of California Medical School, Berkeley.

Schmidt-Nielsen, Bodil M., comparative kidney physiology, Duke University School of Medicine, Durham, N. C.

Singer, Thomas P., oxidative metabolism of sulfur amino acids in animals; and metabolism and function of new coenzymes, Edsel B. Ford Institute for

Medical Research, Henry Ford Hospital, Detroit.

Sprinson, David B., biochemistry of one-carbon intermediates; and biosynthesis of aromatic compounds in bacteria, Columbia University College of Physicians and Surgeons, New York.

Stamler, Jeremiah, experimental atherosclerosis, experimental hypertension, renal function in edema formation, Michael Reese Hospital, Chicago.

Stavitsky, Abram B., studies on the basic mechanisms of antibody production *in vivo* and *in vitro*, Western Reserve University School of Medicine, Cleveland.

Stefanini, Mario, establishment of 'profile' of tests for diagnosis of thrombotic tendency; relation of the endocrine system to the blood coagulation mechanism and the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin in the treatment of thromboembolism, St. Elizabeth's Hospital, Boston.

Stetson, Chandler A., investigations in rheumatic fever, New York University, Bellevue Medical Center, New York.

Szent-Gyorgyi, Andrew Gabriel, studies on structure of myosin, Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Wessler, Stanford, pathogenesis of intravascular thrombosis, Beth Israel Hospital, Boston.

Zweifach, Benjamin William, biochemical analysis of structural elements of blood-tissue barrier, New York University, Bellevue Medical Center, New York.

New Established Investigators

Benesch, Reinhold, role of sulfhydryl and disulfide groups in biological systems, Institute for Enzyme Research, University of Wisconsin, Madison.

Boyle, Edwin, Jr., comparative studies in lipoprotein transport and metabolism concerning atherosclerosis in man, monkey and pig, Medical College of South Carolina, Charleston.

Epstein, Franklin H., metabolic and circulatory factors affecting distribution and excretion of water and electrolytes, Yale University School of Medicine, New Haven, Conn.

Flavin, Martin, Jr., research in enzyme chemistry and intermediary metabolism, New York University College of Medicine, New York.

Foulkes, Ernest Charles, fundamental mechanisms of electrolyte transport across biological membranes, The May Institute for Medical Research, Cincinnati.

Gross, Jerome, structure, composition, genesis, function and malfunction of connective tissues, Robert W. Lovett Memorial Laboratories, Massachusetts General Hospital, Boston.

Kun, Ernest, pathway of the metabolism of hydroxy acids, Institute for Enzyme Research, University of Wisconsin, Madison.

Kuo, Peter T., intravascular distribution of lipid particles in clinical arteriosclerosis, Hospital and School of Medicine, University of Pennsylvania, Philadelphia.

Lazzarini, Abel Alfred, Jr., metabolic and immunological changes occurring in transplanted tissues, New York University Post-Graduate Medical School, New York.

Linker, Alfred, studies on mucopolysaccharides, Columbia University College of Physicians and Surgeons, New York.

Nelson, Clifford Vincent, mechanism of fibrillation; and quantification of the vectorcardiogram, Maine Medical Center, Portland.

Perry, Horace Mitchell, Jr., pathogenesis and treatment of hypertension and atherosclerosis, Washington University School of Medicine, St. Louis.

Schwartz, William B., disorders of electrolyte metabolism and kidney function, Kidney and Electrolyte Laboratory, New England Center Hospital, Boston.

Schweet, Richard S., biological synthesis of protein, Kerckhoff Laboratory of Biology, California Institute of Technology, Pasadena, Calif.

Slade, Hutton Davison, biochemistry of group "A" hemolytic streptococcus, The Rheumatic Fever Research Institute, Chicago.

Spencer, Merrill P., factors affecting distribution of cardiac output, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Thal, Alan Philip, revascularization of the myocardium—an experimental study designed to test the feasibility of a direct suture anastomosis of extracardiac arteries to the coronary arteries; and the mechanism of action of bacteria and bacterial toxins on small blood vessels with particular reference to bacterial shock, University of Minnesota Hospital, Minneapolis.

New Research Fellowships

Adolph, Robert J., effect of digitalis and electrolytes on inotropic properties and ionic exchanges of normal and failing myocardium, University of Illinois, Chicago.

Attinger, Ernst O., correlation of dynamics of pulmonary ventilation and circulation, Boston City Hospital, Boston.

Berman, Herbert Joshua, study of living blood vessels in experimental hypertension and thromboembolism, Boston University, Boston.

Birkhead, Newton Charles, thoracic-aorta blood flow in patients with mitral valve disease and the effect of the valsalva maneuver, Mayo Foundation, Rochester, Minn.

Brady, Allan J., relation between intracellular electrical events and the strength and duration of contraction, University of Washington School of Medicine, Seattle.

Campbell, Edmund West, mechanism of platelets, platelet constituents and allied factors in blood

coagulation and thrombosis, New England Center Hospital, Boston.

Chetrick, Allen, cardiovascular response to exercise in patients with enlarged but otherwise compensated hearts: before and after digitalization, Yale University School of Medicine, New Haven, Conn.

Chidsey, Charles Augustus, III, pulmonary circulation of man in health and diseased states, Bellevue Hospital, New York.

Connor, William Elliott, fat metabolism in atherosclerosis, State University of Iowa College of Medicine, Iowa City.

Cornett, Robert William, cardiovascular adjustments occurring during pregnancy; both normal pregnant women and pregnant women with heart disease will be studied, Boston Lying-in Hospital, Boston.

DeWall, Richard Allison, perfusion techniques as an aid to intracardiac surgery, University of Minnesota Hospitals, Minneapolis.

Feinberg, Harold, myocardial metabolism and relation to coronary flow, Michael Reese Hospital, Chicago.

Gramiak, Raymond, significance of right ventricular outflow tract hypertrophy in valvular pulmonary stenosis, University of Rochester Strong Memorial Hospital, Rochester, N. Y.

Grinnell, Edward Hoepfner, factors which influence myocardial irritability at sub-normal body temperatures, University of Oklahoma School of Medicine, Oklahoma City.

Guze, Lucien B., influence of changes in local tissue pressure on course of pyelonephritis, Yale University School of Medicine, New Haven, Conn.

Guzman, Santiago V., use of molar lactate in treatment of cardiac arrest and slow ventricular rates in complete or incomplete A-V heart block, Philadelphia General Hospital, Philadelphia.

Hancock, Ernest William, physiologic studies in valvular heart disease, Boston City Hospital, Boston.

Lahiry, Nripendra Lal, carbohydrate metabolism in heart tissue, Howard University School of Medicine, Washington, D. C.

Lavender, Ardis Ray, pathogenesis of water and electrolyte disorders in congestive heart failure, University of Chicago Clinics, Chicago.

Lichton, Ira Jay, influence of female sex physiology upon experimental salt and corticoid hypertension, Michael Reese Hospital, Chicago.

Mackoff, Leslie, physiological response to proteolytic enzyme inhibitor found in the alpha-1 and alpha-2 globulins, University of Washington, Seattle.

Maley, Gladys Feldott, mechanism of action of the thyroid hormone, Institute for Enzyme Research, University of Wisconsin, Madison.

Martin, Dan Anderson, effects of life situations and emotions on precipitation and course of congestive heart failure, University of North Carolina School of Medicine, Chapel Hill.

Moskowitz, Merle Seymour, mechanism of estrogen-induced hyperphospholipemia, University of Chicago, Chicago.

Robinson, Roscoe Ross, certain aspects of the hemodynamics and renal function of patients with malignant hypertension, Columbia University, Presbyterian Hospital, New York.

Rosenblum, Robert, factors promoting acute and chronic retention of water in excess of sodium in patients in severe congestive failure, Montefiore Hospital, New York.

Schlant, Robert Carl, measurement of regional blood volume and flows; and studies on the circulatory abnormalities in congenital heart disease and high output failure, Peter Bent Brigham Hospital, Boston.

Ulick, Stanley, relation of aldosterone to edema, College of Physicians and Surgeons, Columbia University, New York.

Wasserman, Fred, use of molar sodium lactate in cardiac resuscitation, Philadelphia General Hospital, Philadelphia.

Wells, Jacques Desmond, reversibility of malignant hypertension with uremia, Cincinnati General Hospital, Cincinnati.

Wetlaufer, Donald Burton, contractile elements of muscle; interactions of metallic ions with myosin, Harvard University, The Biological Laboratories, Boston.

Yeh, Samuel D. J., circulating protein constituents in serum globulins, The Johns Hopkins University School of Medicine, Baltimore.

Renewal Research Fellowships

Brewster, William Russell, Jr., hemodynamic and metabolic interrelationships in activity of epinephrine, norepinephrine, the thyroid hormones and the adrenal cortical steroids, Massachusetts General Hospital, Boston.

Chao, Fu-Chuan, nucleoprotein in yeast, chick embryo and mammalian tissues, Stanford University, Pal Alto, Calif.

Combes, Burton, amino acid and phosphate metabolism in man, Medical Unit, University College Hospital Medical School, London, England.

Done, Alan Kimball, role of pituitary-adrenal system in pathogenesis and treatment of rheumatic fever, University of Utah Medical School, Salt Lake City.

Frazier, Howard Stanley, effect of ouabain and failure on the potassium exchange of the frog ventricle, Harvard Medical School, Boston.

Gordon, Gerald S., investigation of the *in vivo* metabolism of carbohydrate by the heart using glucose C-14; investigation of the mechanism of pulsatile veins and liver in so-called tricuspid insufficiency, Pittsburgh University Medical School, Pittsburgh.

Hatch, Frederick Tasker, program in biochemistry; thesis research on metabolic aspect of a degenerative disease, Massachusetts Institute of Technology, Cambridge.

Huckabee, William Edward, balance of aerobic and anaerobic energy metabolism in body organs as a function of local circulatory adequacy, Massachusetts Memorial Hospitals, Boston.

Killip, Thomas, III, cardio-pulmonary function in obesity, plasma volume changes with exercise in normals and patients with heart disease, New York Hospital, New York.

Knisely, William Hagerman, microscopic observations on living vasculature of mammalian lungs with attention to problems of arteriovenous anastomoses and catheterization, Duke University School of Medicine, Durham, N. C.

Matthews, Edward Carshore, polarographic measurement of tissue oxygen tension, Children's Hospital Research Foundation, Cincinnati.

Nadell, Judith, ionic interchanges and contractility of the heart, Stanford University, Palo Alto, Calif.

Padawer, Jacques, physiology of the mast cell and its relation to cardiovascular disease, Albert Einstein College of Medicine, Yeshiva University, New York.

Reiss, Oscar K., energy metabolism and enzymatic catalysis of the heart muscle, Johns Hopkins University Medical School, Baltimore.

Rudolph, Abraham Morris, pulmonary hypertension in congenital heart disease, Children's Medical Center of Harvard Medical School, Boston.

Schmidt, Willard Carl, study of host response to streptococcal antigens; and immunization of humans with purified streptococcal M protein, Western Reserve University School of Medicine, Cleveland.

Sharp, John Turner, pulmonary edema by measurement of the physical properties of the lungs and airways, Buffalo General Hospital, Buffalo.

Sheppard, Erwin, electrostatic forces involved in blood coagulation and the mode of action of ionic anticoagulants, New York Hospital-Cornell Medical Center, New York.

Walters, Donald H., effect of calcium and magnesium on electrolyte flux across the cellular membrane; kinetic studies as applied to cardiac muscle and the erythrocyte membrane, Harvard Medical School, Boston.

Weissler, Arnold, cardiovascular studies in syncope; arteriovenous glucose differences in the extremities, Duke University School of Medicine, Durham, N. C.

Continued Research Fellows

Finnerty, Frank A., Jr., investigations on toxemia of pregnancy, studies on the cerebral and cardiac hemodynamics in postural hypotension; cerebral and cardiovascular studies during hypotensive and freezing "anesthesia", Georgetown Medical Division, District of Columbia General Hospital, Washington, D. C.

Nanninga, Luddo B., binding of ions to heavy and light meromyosin and to myosin binding of adenosine, adenine, ATP, ADP, etc. to the same proteins, Institute for Muscle Research, Woods Hole, Mass.

NOTICE TO CONTRIBUTORS

Contributors to CIRCULATION are requested by the Editor-in-Chief to supply duplicate manuscripts, tables and illustrations to facilitate selection and processing of papers.

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† Deceased March 21, 1955

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Continued on page 480

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Continued from page 479

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Consultant, Section of Medicine, Mayo Clinic; Assistant Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

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Assistant Director, Chest Department, Michael Reese Hospital; Associate Attending Physician, Winfield Hospital; Consultant Physician in Charge, Pulmonary Physiology Laboratory, Municipal Tuberculosis Sanatorium of Chicago, Chicago, Ill.

LOUIS A. SOLOFF, M.D.

Clinical Professor of Medicine, Temple University Medical School and Hospital; Chief of Medicine, Episcopal Hospital, Philadelphia, Pa.

HERBERT M. STAUFFER, M.D.

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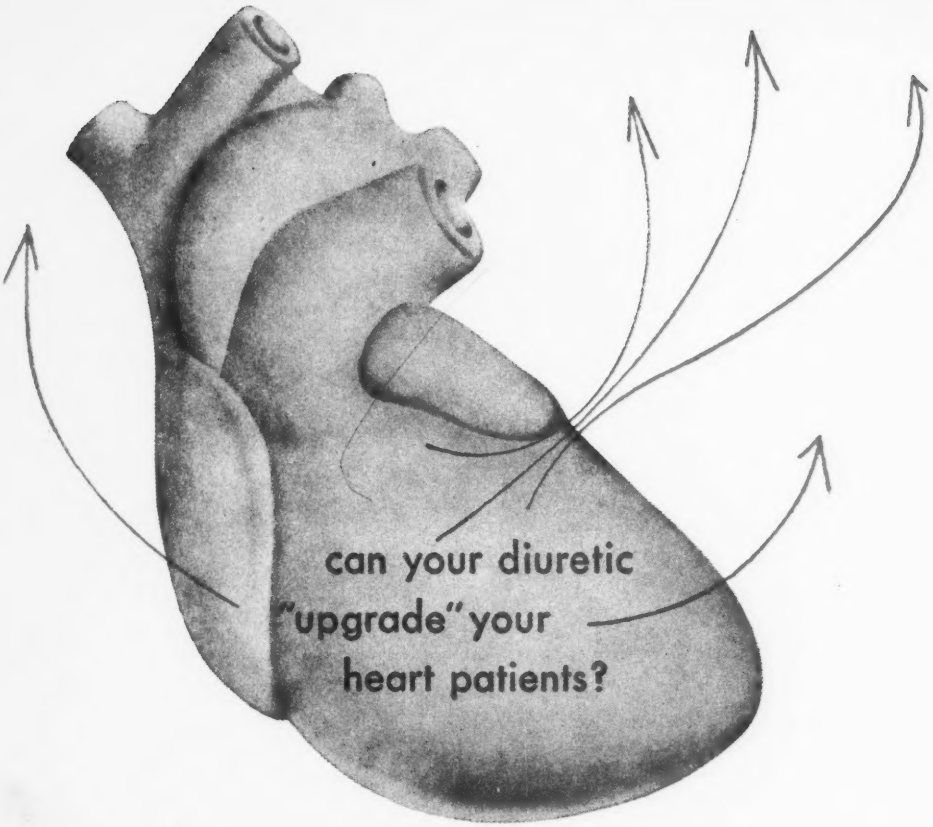

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